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# **The association between impaired fetal growth and neurodevelopment in childhood**



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**University College**

**Michaelmas Term, 2015**

*Thesis submitted in partial fulfilment of the degree of Doctor of Philosophy at the University  
of Oxford*

**Department of Psychiatry**

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Elizabeth Murray, University College, Michaelmas Term 2015

### **Abstract**

Impaired fetal growth is associated with an increased risk of negative neurodevelopmental outcomes. The majority of research to date, however, has relied on birth weight as an index of fetal growth impairment. Furthermore, few studies have included samples from low- and middle-income countries (LMICs). The objective of this thesis was to examine the association between impaired fetal growth, using a range of birth indices, and neurodevelopment in childhood.

A systematic review showed that cognitive development and attention are two domains particularly affected by impaired fetal growth and thus was the focus of this thesis. Cognitive development and attention were assessed in three large, prospective birth cohorts drawn from high-, middle- and low-income countries: Pelotas (Brazil) 2004 (N=3579), ALSPAC (UK) (N=7354) and INTERGROWTH-21<sup>st</sup> (UK, Italy, Brazil, India and Kenya) (N=1073). INTERGROWTH-21<sup>st</sup> only enrolled low-risk mothers, whereas Pelotas and ALSPAC were not selective. In all three cohorts, indices of birth weight, stunting, wasting and asymmetry were collected at birth. Attention was assessed using subscales of the Child Behaviour Checklist or the Strengths and Difficulties Questionnaire; and cognition was assessed using the Wechsler Preschool and Primary Scales of Intelligence-Revised or INTERGROWTH-21<sup>st</sup> Neurodevelopmental Assessment (INTER-NDA). Each cohort measured these outcomes at one time point (range = 2-6 years of age). As part of this thesis the INTER-NDA was validated against the Bayley Scales of Infant Development.

Associations between birth anthropometric indices and both cognitive and attention outcomes were assessed using hierarchical ordinal logistic regression. Attention impairment was associated with stunted birth length (BL) but only in females (OR=1.21-1.69,  $p<.05$ ), across cohorts drawn from high-, middle- and low-income countries. In contrast, cognitive impairment was associated with stunted head circumference (HC) and low ponderal index (PI) in both sexes, although predominantly in LMIC settings (HC: OR=1.73-1.91,  $p<.05$ ; PI: OR=1.46-4.91,  $p<.05$ ).

Identification of a female-specific association between stunted BL and poor attention across cohorts from different settings, suggests the association is robust to differential confounding effects. In contrast, the stronger association in LMICs between cognitive impairment and stunted HC and low PI suggests confounding structures (e.g. maternal and neonatal health care) may modify the effect of fetal growth on cognitive development. Birth indices (specifically BL, HC and PI) may be particularly helpful in identifying children at risk of neurodevelopmental impairment for early intervention.

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## **Role of the candidate**

The primary cohort I worked with was the INTERGROWTH-21<sup>st</sup> cohort. I conducted the systematic review of the effects of fetal growth impairment on neurodevelopment in childhood, to help determine which neurodevelopmental assessments to include in the two-year follow up of the INTERGROWTH-21<sup>st</sup> Project. Following this, I added the attention subscale of the CBCL to the two-year follow up. I oversaw translation into Italian, Portuguese, Hindi and Marathi for use and dissemination in all INTERGROWTH-21<sup>st</sup> neurodevelopment sites (UK, Italy, Brazil, Kenya and India). I participated in the collection of the two year assessment data, conducting two year follow-up assessments at the Oxford site. I was trained in the administration and scoring of the Bayley Scales of Infant Development, 3<sup>rd</sup> edition (BSID-III) and conducted the validation of the INTER-NDA against the BSID-III in a sample of 88 children.

To further answer my research questions and supplement data obtained from the INTERGROWTH-21<sup>st</sup> Project, I analysed secondary data from the ALSPAC and Pelotas 2004 birth cohorts to contribute to my analysis. As part of this I spent I also spent one month in Pelotas, Brazil at the Universidade Federal de Pelotas, in the Epidemiological Research Centre. I worked within the 2004 Birth Cohort team on a number of publications and data analyses. For the ALSPAC analysis, I spent time at the University of Bristol, in the School of Social and Community Medicine with the ALSPAC research team there.

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**List of Abbreviations**

|                              |                                                                                    |
|------------------------------|------------------------------------------------------------------------------------|
| AC                           | Abdominal circumference                                                            |
| ADHD                         | Attention-deficit/hyperactivity disorder                                           |
| AGA                          | Appropriate-for-gestational-age                                                    |
| ALSPAC                       | Avon Longitudinal Study of Parents and Children                                    |
| ANOVA                        | Analysis of variance                                                               |
| APGAR                        | Appearance -pulse-grimace-activity-respiration                                     |
| AUC                          | Area under the curve                                                               |
| BL                           | Birth length                                                                       |
| BMI                          | Body mass index                                                                    |
| BPD                          | Biparietal diameter                                                                |
| BSID                         | Bayley Scales of Infant Development                                                |
| BW                           | Birth weight                                                                       |
| CANS                         | Clinical Assessment of Nutritional Status                                          |
| CBCL                         | Child Behaviour Checklist                                                          |
| CBQ                          | Child Behaviour Questionnaire                                                      |
| CRL                          | Crown-rump length                                                                  |
| DOHaD                        | Developmental Origins of Health and Disease                                        |
| FCR                          | Fetal circulatory redistribution                                                   |
| FGLS                         | Fetal Growth Longitudinal Study                                                    |
| FL                           | Femur length                                                                       |
| fMRI                         | Functional magnetic resonance imaging                                              |
| FSIQ                         | Full-scale intelligence quotient                                                   |
| GA                           | Gestational age                                                                    |
| HC                           | Head circumference                                                                 |
| HIC                          | High-income country                                                                |
| HPA                          | Hypothalamic-pituitary-adrenal                                                     |
| ICC                          | Intra-class correlation                                                            |
| INTERGROWTH-21 <sup>st</sup> | International Fetal and Newborn Growth Consortium for the 21 <sup>st</sup> Century |
| INTER-NDA                    | INTERGROWTH-21 <sup>st</sup> Neurodevelopmental Assessment                         |
| IUGR                         | Intrauterine growth restriction                                                    |
| LIC                          | Low income country                                                                 |

|         |                                                                |
|---------|----------------------------------------------------------------|
| LMIC    | Low- and middle-income country                                 |
| LBW     | Low birth weight                                               |
| LMP     | Last menstrual period                                          |
| MCA     | Middle cerebral artery                                         |
| MGRS    | Multicentre Growth Reference Study                             |
| MRI     | Magnetic resonance imaging                                     |
| NCSS    | Newborn Cross-Sectional Study                                  |
| NHS     | National Health Service                                        |
| NPV     | Negative predictive value                                      |
| PI      | Ponderal index                                                 |
| PIQ     | Performance intelligence quotient                              |
| PPV     | Positive predictive value                                      |
| OLR     | Ordinal logistic regression                                    |
| OR      | Odds ratio                                                     |
| REGWQ   | Ryan-Einot-Gabriel-Welsch Range                                |
| ROC     | Receiver-operating characteristics                             |
| SD      | Standard deviation                                             |
| SDQ     | Strengths and Difficulties Questionnaire                       |
| SGA     | Small-for-gestational-age                                      |
| SMD     | Standardised mean difference                                   |
| SPSS    | Statistical Package for the Social Sciences                    |
| UA      | Umbilical artery                                               |
| UNICEF  | United Nations International Children's Emergency Fund         |
| VEP     | Visual evoked potential                                        |
| VIQ     | Verbal intelligence quotient                                   |
| WHO     | World Health Organization                                      |
| WISC    | Wechsler Intelligence Scale for Children                       |
| WPPSI-R | Wechsler Preschool and Primary Scale of Intelligence - Revised |

### Publications associated with this work

Murray, E., Fernandes, M., Fazel, M., Kennedy, S. H., Villar, J., & Stein, A. (2015). Differential effect of IUGR on neurodevelopment in childhood: a systematic review. *British Journal of Obstetrics and Gynaecology*, 122(8), 1062-72. doi: 10.1111/1471-0528.13435.

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Murray, E., Matijasevich, A., Pearson, R., Santos, I. S., Barros, F. C., Victora, C., Stein, A. (2015). Are fetal growth impairment and preterm birth causally related to child attention problems and ADHD? Evidence from a comparison of high- and middle-income cohorts, *Journal of Epidemiology and Community Health*, in press.

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# **1 General introduction**

## **Chapter outline**

### **1.1 Chapter overview**

### **1.2 Fetal growth impairment**

- 1.2.1 The use of birth anthropometric indicators to assess fetal growth
- 1.2.2 Growth standards and growth references
- 1.2.3 Limitations of birth weight as an indicator of fetal growth
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- 1.3.1 Cognitive and attention development and function
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- 1.3.3 Effect of impaired fetal growth on neurodevelopment
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### **1.5 The confounding effects of preterm birth**

### **1.6 The importance of studying populations from low- and middle-income countries**

### **1.7 Gaps in the literature**

### **1.8 Aims of the research**

- 1.8.1 Research hypotheses

### **1.9 Structure of the thesis**

### **1.10 References**

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## **1.1 Chapter overview**

The overall aim of this thesis is to examine the association between impaired fetal growth and neurodevelopment in childhood. Disturbed neurodevelopment in childhood represents a significant global burden of disease and is associated with a number of negative long-term outcomes. There are many pre- and postnatal factors that increase the risk of poor neurodevelopmental outcomes, one of which is impaired fetal growth leading to small size at birth. As measurements taken at birth are widely collected and easily obtained, they are a useful tool for identifying children at risk of poor neurodevelopmental outcomes. The focus of this thesis, therefore, is the association between impaired fetal growth, measured by anthropometric indices, taken at birth, and neurodevelopment in childhood. Attention and cognitive development, following a systematic review of the literature (Chapter 2) have been selected as the neurodevelopmental outcomes on which this thesis will primarily focus. This is because these two domains were shown to have the strongest association with poor fetal growth, compared to the other domains examined.

This introductory chapter will provide a review of the literature on the association between fetal growth impairment and neurodevelopment in childhood. Based on the chronology of events in the association (i.e. fetal growth preceding child neurodevelopment), fetal growth concepts will be introduced first (including terminology, measurement issues, assumptions, considerations, limitations, and risk factors), followed by neurodevelopment concepts (including risk factors, long-term consequences, underlying neurobiology, the effect of impaired fetal growth on neural development and key considerations in neurodevelopmental assessments). Other important points for consideration, such as the effects of preterm birth and the importance of studying populations from low-income countries (LICs), will also be introduced. The chapter will conclude with gaps in the literature, the aims and hypotheses of the thesis and a detailed description of the remainder of this thesis.



## 1.2 Fetal growth impairment

Fetal growth impairment, a major public-health problem, is the second leading cause of perinatal mortality and morbidity worldwide, second only to preterm delivery<sup>1</sup>. As fetal management techniques improve, fetuses that may not have survived in the past are now surviving to delivery and beyond, thus contributing to increased morbidity<sup>2</sup>. Fetal growth impairment is now estimated to complicate 10-15% of all pregnancies, dependent on population characteristics and geographical location<sup>3</sup>. Although the burden of fetal growth impairment is of significant concern in high-income countries (HICs), the burden is increased in low- and middle-income countries (LMICs)<sup>4</sup>. By region, the burden of fetal growth impairment is concentrated mainly in south-central Asia, accounting for 75% of all fetal growth impairment cases worldwide, followed by Africa (20%) and Latin America (5%)<sup>5</sup> (Figure 1.1).

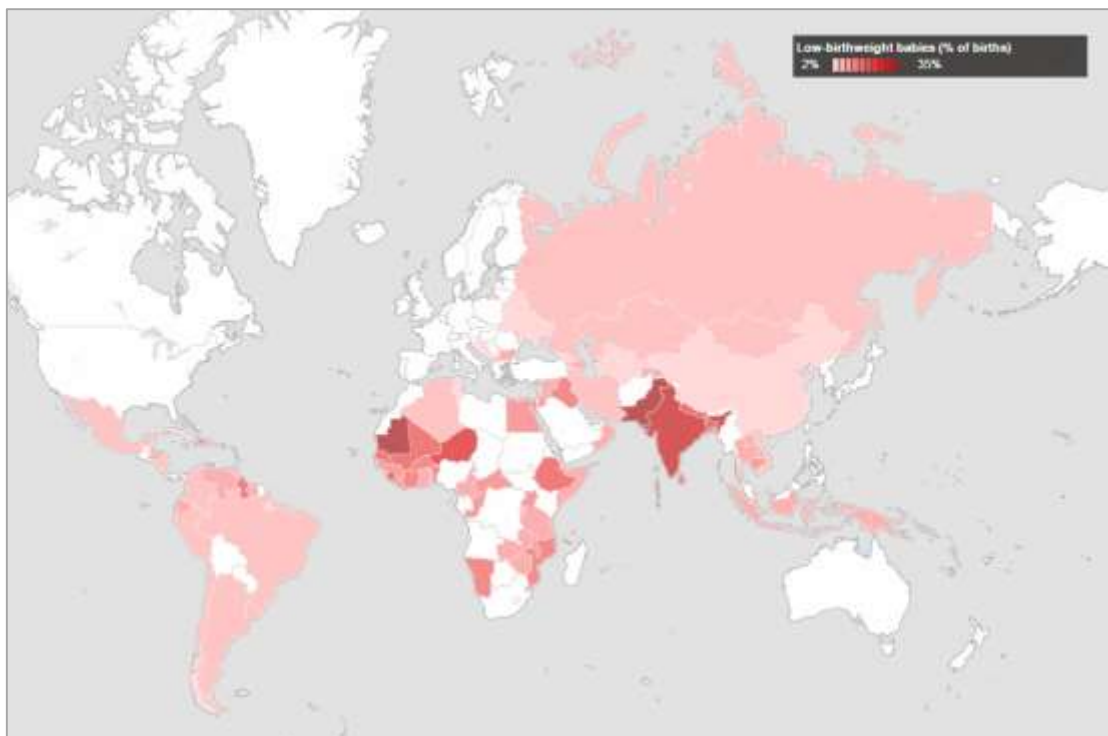


Figure 1.1. Global prevalence of low birth weight babies (% of births) 2010-2014<sup>6</sup>



### **1.3 The use of birth anthropometric indicators to assess fetal growth**

An important tool for assessing impaired fetal growth is the use of anthropometric measurements at birth. Anthropometry is the most universally applicable, inexpensive and non-invasive method available to assess size, proportions and composition of the human body<sup>13</sup>. Although the gold standard for identifying impaired fetal growth is through in utero ultrasound assessments, such as serial ultrasound or Doppler velocimetry, many LICs do not have the resources or medical infrastructure to routinely conduct serial ultrasound. As such, anthropometric measurements, taken at birth, provide a useful single-point retrospective snapshot of the fetal growth process<sup>13</sup>. An infant's size at birth reflects the average growth rate in utero, and although fetal growth does not occur linearly, with periods of slow and accelerated growth, small size at birth can be a useful indicator that an infant has failed to reach its growth potential.

The use of anthropometry as an indicator of optimal physical development requires an understanding of the organisation of the levels of human body composition. The conceptual model relating anthropometry to body composition (the five-level model of body composition; Figure 1.3) provides insight into the physiological mechanisms represented by anthropometric measurements<sup>14</sup>.

The central tenet of the five-level model of body composition is that there is a quantitative relationship between compartments across levels (and also within levels), that remains constant over a specified time (usually months or years)<sup>14</sup>. Anthropometric measurements made at whole-body level (Level V) can therefore be used to derive information about tissue-level components (Level IV), such as skeletal size and adiposity. Some commonly used birth anthropometric indices for relating whole body measurements to tissue-level components include BW (a measure of total body mass), birth length (BL; a measure of skeletal length), head circumference (HC; a skeletal measure that correlates with total brain volume at

$r=.0.93^{15}$ ) and weight-for-length (indices that correlate with adiposity at  $r=.70^{16}$ ). This thesis will examine measurements taken at the whole-body level (Level V), which will be used as a proxy measure for Level IV components, such as adipose tissue and skeletal measurements.

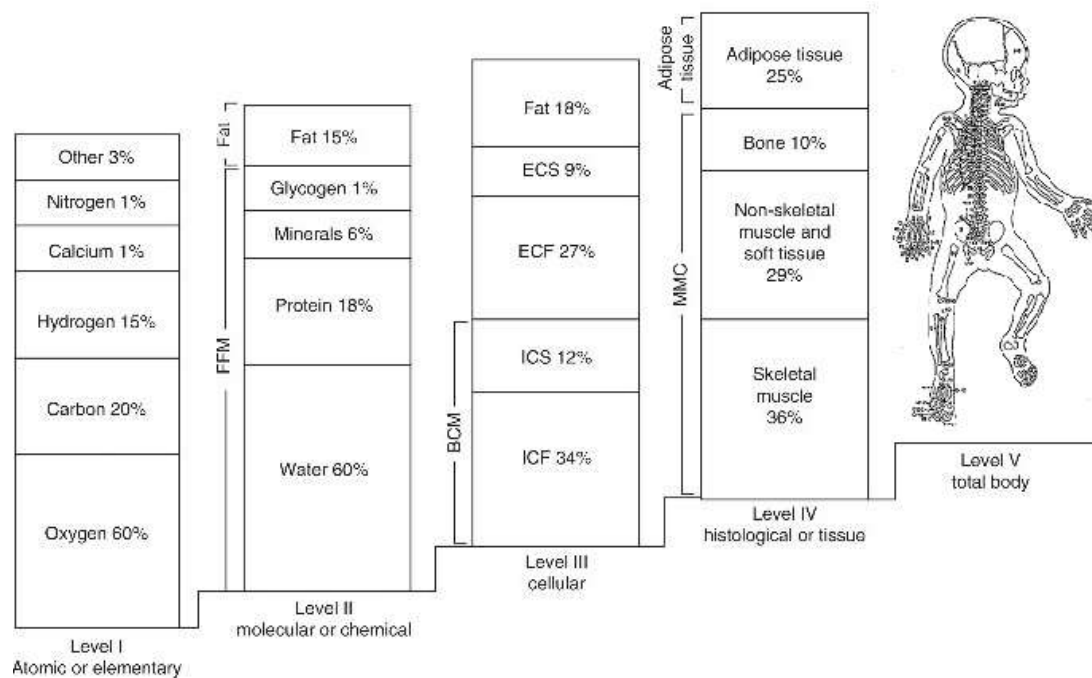


**Figure 1.3. Five level model of body composition in childhood. ECF: extracellular fluid; ICF: intracellular fluid; BCM: ICF+ICS: body cell mass; FFM: fat-free mass; BLM: body-lean mass; ECS: extracellular solids; ICS: intracellular solids. Adapted from Jiménez (2013)<sup>17</sup>**

### 1.3.1.1 Anthropometric measurements, indices and indicators

The terms anthropometric ‘measurements’, ‘indices’ and ‘indicators’ are often misused or used interchangeably, however it is important to define key features and differences between the terminology for use in the current thesis. Common anthropometric measurements include birth weight (BW), birth length (BL) and head circumference (HC). Indices are created from

combinations of measurements. They are essential for the interpretation of measurements: for example length (or height) alone is meaningless unless it is related to an individual's age or sex<sup>18</sup>. Common examples of birth anthropometric indices include weight-for-age, such as small-for-gestational age (SGA), height-for-age, and weight-for-height, such as body mass index (BMI;  $\text{weight}/(\text{height} \times \text{height})$ ) or ponderal index (PI;  $\text{weight}/(\text{height} \times \text{height} \times \text{height})$ ). These indices alone provide little information unless related to reference data (discussed in more detail below), which can provide information about the size of the neonate compared to a reference group. Indices can be expressed as Z-scores, percentiles or percent of median, against a reference population. Percentiles are commonly used in research settings due to ease of interpretation, and represent the percentage of the population or sample that the individual equals or exceeds. As such, examining groups that fall below a particular percentile represents a 'statistical' (as opposed to clinical) definition of fetal growth impairment. It must be acknowledged that a portion of children who fall below a percentile will be 'normally grown', but constitutionally small.

The term 'indicator' refers to the use or application of indices. An indicator is often constructed from indices, for example birth anthropometric indices function as indicators of body composition and size. A valid indicator owes a substantial portion of its variation to that which it purports to indicate.

### **1.3.2 Growth standards and growth references**

Before further discussion, it is necessary to distinguish between growth *references* and growth *standards*. The current thesis will assess indices of fetal growth against a current growth reference (the United States Reference for Fetal Growth)<sup>19</sup>, and two growth standards, one derived from the Multicentre Growth Reference Study (MGRS)<sup>20</sup> and the other from the INTERGROWTH-21<sup>st</sup> Fetal Growth Longitudinal Study (INTERGROWTH-21<sup>st</sup>)<sup>21</sup>.

Growth references provide a common basis for comparing populations, generally derived from a geographically-homogenous reference population. Provided reference populations are large enough to contain adequate statistical information and the population is reasonably healthy enough to avoid major distortions, growth references are adequate for comparative purposes<sup>13</sup>. Before the establishment of fetal and child growth standards, growth reference curves were used widely (there have been 104 published since 1990). The United States National Reference for Fetal Growth<sup>19</sup>, which was derived from the live birth files of 3.8 million births in the United States, is a widely used weight-for-age reference. Although a large population-based sample was used in deriving these growth curves, a methodological limitation was identified in the number of discrepancies around the estimation of last menstrual period (used to determine gestational age; GA).

References vary between countries and populations, and as such, the meaning of the indicators derived from growth reference curves is of little validity in samples drawn from populations other than that of the reference. As the majority of growth reference charts are derived from HIC populations, they are of limited use in populations from LMICs. For example, an Indian infant may be at the 10<sup>th</sup> percentile of length-for-age according to Swedish growth references, but at the 60<sup>th</sup> percentile according to Indian growth references. This child would be misclassified as SGA using the Swedish growth reference, when it is, in fact, normally grown for its population.

Since initiation by the WHO in 1997<sup>22</sup>, there has been a significant investment in the establishment of international growth *standards*, drawn from multiple, geographically and culturally diverse populations for evaluating indices of fetal growth. Growth standards incorporate the concept of 'optimal growth'. They illustrate the growth trajectory that should be attained in the absence of factors negatively affecting growth, and allow a comparison between attained growth and growth 'potential'. Two international growth standards, drawn

from the MGRS<sup>20</sup>, covering the period from birth to 5 years of age, and the INTERGROWTH-21<sup>st</sup> Project<sup>21</sup>, covering growth from 14 weeks GA to birth, have now been established to identify sub-optimal growth against universal norms. As these standards are both included for comparison in the current thesis, the relative methodological strengths and weaknesses of each will now be briefly introduced.

### **1.3.2.1 The Multicentre Growth Reference Study (MGRS) growth standards**

The MGRS was a community-based international project, which combined longitudinal data from birth to 24 months in a study of children aged 18 to 71 months. The pooled sample was drawn from six participating countries (Brazil, Ghana, India, Norway, Oman and the United States), and included approximately 8,500 children. Children were admitted to the study based on low-risk of growth impairment, including the absence of health or environmental constraints on growth, adherence to MGRS feeding recommendations (breastfeeding for 12 months), absence of maternal smoking, single term birth and absence of significant morbidity. Children were screened and enrolled at birth and then visited at home a total of 21 times up to 23 months post-natal age. A number of standards were created from the MGRS including weight-for-age, length-for-height, and head circumference-for-age, separately for boys and girls.

To date, over one hundred countries have adopted the MGRS growth curves as standards of optimal growth<sup>23</sup>. A limitation of the birth anthropometric index standards from the MGRS is that birth is considered as 'time zero', and does not account for variation in GA at birth. Although infants were excluded if they were born <37 or ≥42 weeks GA, fetuses continue to grow throughout this period, and infants born at 37<sup>+1</sup> weeks GA will fall significantly below those born 41<sup>+6</sup> weeks GA on the MGRS growth standards, reflecting variations in timing of delivery.

### **1.3.2.2 The International Foetal and Newborn Growth Consortium for the 21<sup>st</sup> Century (INTERGROWTH-21<sup>st</sup>) growth standards**

INTERGROWTH-21<sup>st</sup> standards were derived from eight geographically diverse countries, including Brazil, China, India, Italy, Kenya, Oman, UK and USA. Their development was aimed at complementing the MGRS, and was based on the same conceptual framework. Women were selected into the study on the basis of posing low-risk for preterm delivery and intrauterine growth restriction (IUGR), including being of normal age, BMI, height, no known morbidity, no socio-economic constraints, no alcohol or smoking during pregnancy and no known previous obstetric complications. Standards of newborn weight, length and HC were derived from 20 468 pregnancies<sup>24</sup>.

INTERGROWTH-21<sup>st</sup> growth standards differ from MGRS standards in that they account for variation of GA at birth (33-42 weeks GA). Therefore, neonates who fall, for example, at the 10<sup>th</sup> percentile on the INTERGROWTH-21<sup>st</sup> newborn charts will be at the 10<sup>th</sup> percentile of optimal size for their GA at birth. In contrast, neonates who fall at the 10<sup>th</sup> percentile on the MGRS newborn chart will be at the 10<sup>th</sup> percentile of optimal size at birth, regardless of GA.

Importantly, however, the use of INTERGROWTH-21<sup>st</sup> charts require accurate estimation of GA (usually by ultrasound early the second trimester in combination with timing of last menstrual period; LMP). The routine use of ultrasound, is not common in LICs however<sup>13</sup>, so in cases where GA cannot be accurately estimated then MGRS charts with absolute cut-offs may be preferential.

### **1.3.3 Limitations of birth weight alone as an indicator of fetal growth**

Although pediatric medicine has moved away from weight or weight-for-age indices to characterise growth in childhood, due to inherent limitations, obstetric practice and research still largely rely on BW indices as meaningful retrospective measures of fetal growth<sup>25</sup>. Birth weight is a measurement of the combined mass of all bodily components, including muscle,



bone, organs, blood, and adipose tissue (Figure 1.4). Anthropometric BW indices include low birth weight (LBW; considered to be neonates with BW <2500g<sup>26</sup>) and SGA, generally <10<sup>th</sup> percentile for age and sex relative to population-based standard curves<sup>3</sup>.

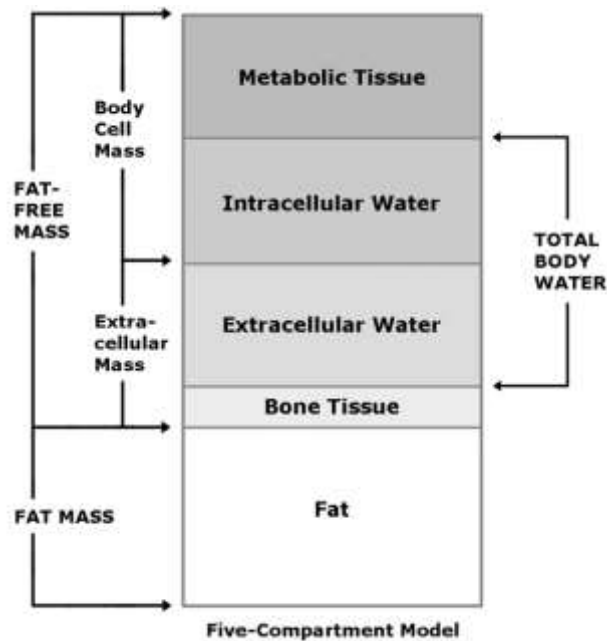


**Figure 1.4. The major components of body weight**

BW indices have been suggested to be an imprecise method of identifying and describing neonates with impaired fetal growth<sup>27</sup>. Classifications of growth impairment that rely on BW alone fail to capture the nuanced growth phenotype (the specific ways in which growth impairment has affected various bodily dimensions)<sup>28</sup>. For example a neonate with adequate skeletal growth but low adiposity may attain the same BW as a neonate with high adiposity but impaired skeletal growth. Studies examining the long-term outcome of fetal growth impairment based solely on BW or SGA are thus likely to include a largely heterogeneous sample of infants

(as the same weight can be obtained from any number of fetal growth patterns<sup>29</sup>). This heterogeneity is likely to have contributed to inconsistencies in the current literature<sup>1</sup>.

#### **1.3.4 Alternative indicators of fetal growth impairment: stunting and wasting**

Recent research has called for traditional BW-based classifications of fetal growth to be replaced with a more precise description of the way in which growth has been affected<sup>25</sup>. This would allow the capture of information about the timing of fetal growth impairment, as well as the nutritional status of the neonate<sup>13</sup>. Several publications have developed the concepts of two primary phenotypes of fetal growth impairment, analogous to childhood ‘stunting’ and ‘wasting’<sup>30,31</sup>.

Stunting and wasting are commonly used in pediatrics as indicators of different types of child growth impairment. Stunting, also referred to as Type 1, symmetric or proportionate growth restriction, is identified by skeletal anthropometric indices. Examples of such indices included short length-for-age or small HC. A small HC is considered to represent symmetric growth restriction as it reflects proportionally decreased skeletal growth sustained throughout the course of fetal development<sup>32</sup>. Wasting, also referred to as Type 2, asymmetric or disproportionate growth restriction, reflects a decrease in fetal adiposity. Wasting can be identified by low weight-for-length measures, such as PI or BMI. Stunting and wasting are fundamentally distinct anthropometric phenotypes which have been shown arise from different timings and durations of intrauterine insult<sup>32</sup>. Furthermore, these fetal growth phenotypes have been shown to have different placental characteristics<sup>33,34</sup>, risk factors<sup>25</sup>, distribution across populations<sup>32</sup>, neonatal morbidity<sup>35</sup>, mortality<sup>25,36</sup>, and post-natal growth characteristics<sup>37</sup>.

Before going further, it is important to clarify the terms used and how they relate to underlying concepts of fetal growth impairment and body composition. The terms ‘stunting’ and ‘wasting’ represent *processes*<sup>18</sup>. Stunting indicates a process of slowing skeletal growth, and a significant degree of stunting represents the accumulated consequences of impaired growth

over time<sup>13</sup>. 'Stunting', used in this context, refers to anthropometric indicators of impaired skeletal growth. Commonly used skeletal indicators include BL and HC, which have been included as indicators of stunting in the current thesis. Stunting, used in this context, should be distinguished from the common use of the term 'stunting' in pediatric literature, a clinical term specifically referring to an infant or child with short height-for-age. In contrast to stunting, wasting indicates a process of either failure to gain weight or of weight loss, which generally reflects a more acute insult<sup>18</sup>. Wasting at birth is commonly measured by weight-for-length indices of PI and BMI.

PI is calculated according to Rohrer's index, and is birth weight/height<sup>3</sup>, whereas BMI is birth weight/height<sup>2</sup>. There is debate as to which of these is the most appropriate index of wasting at birth, and both have been shown to be dependent on age until adolescence. Historically, PI was used as the primary indicator of neonatal adiposity, and is still commonly used and published as an adverse pregnancy outcome<sup>38</sup>, an indicator of poor fetal growth<sup>39</sup>, an indicator of disproportionate fetal growth<sup>40</sup>, and predicted from populations-based growth reference charts<sup>41</sup> (all 2015 publications). PI has been shown to be a good correlate of total percent body fat and skin-fold thickness<sup>42,43</sup>, established adiposity indicators.

BMI, however, is growing in popularity as a marker of neonatal wasting<sup>25</sup>, as it allows meaningful comparisons with studies examining BMI in childhood. Some studies have combined outcomes, using PI as an indicator of adiposity from birth to two years, and then BMI from two years onwards<sup>44</sup>. There have been very few studies, however, that have directly compared PI and BMI. One study showed that PI and BMI are both better predictors of negative health outcomes than other parameters used to assess overweight<sup>45</sup>, and one study suggested that PI provides a better indicator of adiposity (as it is not correlated with BL) up to 39 weeks GA, beyond which BMI is the preferred indicator<sup>46</sup>. Due to these controversies, the current research has included both PI and BMI as indicators of adiposity at birth.

Although 'wasting' has commonly been used interchangeably with asymmetric growth restriction, for the purposes of this thesis, the term 'wasting' has been restricted to indices of adiposity (PI and BMI). Indices of asymmetry (proportionality ratios between HC, BL, PI and BMI) have been examined separately (discussed further below), as very little research has been done to date on these indices.

#### **1.3.4.1 Risk factors and underlying pathogenesis of stunting and wasting**

Universal risk factors for impaired fetal growth include low maternal education level, maternal undernutrition (low maternal BMI), abnormal obstetric history, and conditions such as epilepsy, preeclampsia and eclampsia, which have a wide range of severities, presentation and timing during pregnancy. These have been shown to have similar strength of association with both stunting and wasting<sup>25</sup>. Some risk factors, however, have been independently linked to stunting or wasting, and relate to the underlying pathogenesis associated with the different growth phenotypes.

Stunting is thought arise from the combination of a number of risk factors sustained throughout pregnancy, such as smoking and illicit drug use<sup>25</sup>, or the presence of more severe risk factors such, as genetic disorders, dwarf syndromes, congenital viral infections, and metabolic insufficiency<sup>47</sup>. These factors diminish the rate of cell division during early gestation, and proportionally decrease skeletal-based measurements of length and HC of the developing fetus. This results in sustained, linear growth restriction throughout the course of fetal development<sup>32</sup>.

Risk factors for wasting, however, have been shown to differ from those for stunting. Whereas stunting primarily arises from sustained risk factors throughout gestation, wasting at birth is thought reflect intrauterine insult in the last trimester of pregnancy, a period characterized by the advancing accretion of adipose tissue<sup>48</sup>. Specific risk factors for wasting include uteroplacental function, including chronic hypertension and diabetes, or temporary

nutritional deficit<sup>47</sup>, but can also result from transitory insults to the intrauterine environment such as maternal infection<sup>18</sup>.

Asymmetric measurements at birth are thought to arise from a very specific set of intrauterine conditions. Asymmetric growth, where the BL, PI or BMI are reduced relative to the HC (i.e. a high HC/BL ratio), is thought to arise from fetal circulatory redistribution (FCR), a defensive hemodynamic adaptation. The FCR process involves the preferential redistribution of blood flow to the brain<sup>49</sup>, at the cost of substrate availability in the liver and other downstream organs<sup>50-52</sup>. Indices of asymmetry are derived from proportional measurements (such as HC/BL, HC/PI or HC/BMI), whereby FCR may lead to a large HC relative to a lower BL, PI or BMI at birth.

FCR has historically been referred to as 'brain sparing', in which fetal circulatory adaptation is thought to protect neural development<sup>53</sup>. This assumption of 'protection' however has been recently challenged<sup>54,55</sup>. Whilst FCR may maintain adequate cerebral oxygenation and thus be favourable for overall fetal survival, it may not compensate for impaired neurodevelopmental outcome<sup>56</sup>. Some research suggesting it may actually confer a *higher* risk of neural insult in both humans<sup>54,55</sup> and animals<sup>57</sup>. As such, whether FCR indeed has neuroprotective effects remains a topic of debate<sup>58</sup>.

#### **1.3.4.2 Global distribution of stunting and wasting**

There are few studies that have looked at the prevalence of stunting and wasting at birth across different geographies. As such, inferences on the geographical distribution of stunting and wasting at birth are commonly drawn from aggregated data on children<sup>18</sup>. Recent estimates from a joint database of UNICEF, the WHO and the World Bank<sup>59</sup> show geographical variation in the prevalence of stunting and wasting in children younger than 5. Globally, 162 million (25%) children under 5 years were stunted in 2012. A recent Lancet paper<sup>60</sup> that showed that 90% percent of all stunted children worldwide are concentrated in 36 countries with 56% of in Asia (91 million) and 36% in Africa (58 million). Within-country variation was also identified, with the

prevalence of stunting highest for the poorest segments of the population. A map of the distribution of child stunting is presented in Figure 1.5.

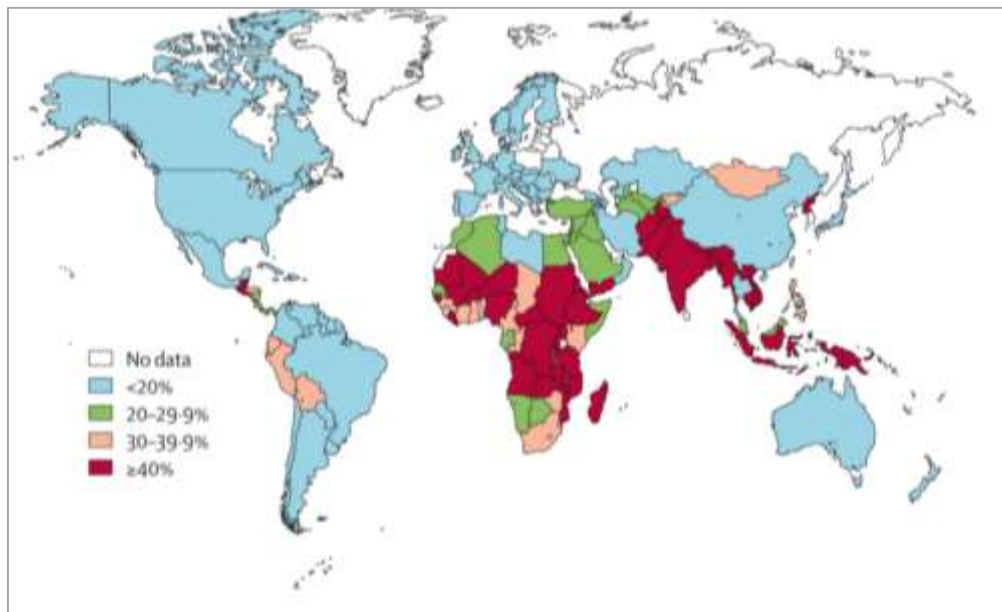


**Figure 1.5. Global prevalence of stunting in children under 5 years**

The global estimate of wasting or severe wasting was 68 million (11%) children under the age of 5. Seventy percent of wasted children lived in Asia (48 million) and 28% in Africa (19 million)<sup>61</sup>. An analysis was also conducted of the overlapping distribution of stunting and severe wasting<sup>60</sup> in a subset of Asian, African, Latin American and Caribbean populations. Severe wasting was not accompanied by stunting in the majority of younger children (80-100%), however was moderately comorbid in older children (40-50%). It was concluded that stunting and wasting are not necessarily associated on a geographical basis, providing further support for a disaggregation of growth indicators in two separate growth phenotypes at birth. These

findings confirmed those of an early study that identified that countries with a similar stunting prevalence can have a several-fold difference in the prevalence of severe wasting<sup>62</sup>.

#### **1.3.4.3 Previous research on outcomes associated with stunting and wasting**

Stunting and wasting have also been shown to have different morbidity and mortality outcomes. In pediatric literature, severe wasting has been suggested to lead to a higher risk of mortality than severe stunting<sup>60,63</sup>, although the mortality rate is similar when milder cases of stunting and wasting are considered<sup>60</sup>. Global estimates from 2004 showed stunting accounted for 1.4 million deaths worldwide (14.5% of deaths in all children under the age of 5 years old) and wasting accounted for 1.5 million deaths (14.6% of all deaths in children under the age of 5 years old).

There are also differences in the morbidity outcomes associated with stunting and wasting. This is important because it suggests there may also be differences in neurodevelopmental outcomes. A recent study identified wasting to be associated with an increased risk of short-term morbidity in the neonatal period, including admission to the neonatal intensive care unit, no oral feeding for more than 24 hours, respiratory distress syndrome and transient tachypnea<sup>25</sup>. Although no studies have compared the long-term outcomes associated with stunting and wasting at birth, studies examining the long-term outcomes of stunting and wasting in childhood have suggested that stunting, more than wasting, is a risk factor for lower cognitive performance and less years of education, lower income and fewer household assets, and increased blood pressure<sup>64</sup>. Taken together, these findings suggest that whilst wasting may increase the risk of short-term morbidity, particularly in neonatal outcomes, stunting may increase the risk for negative long-term outcomes, such as child cognitive and attention development. This hypothesis will be tested in Chapter 5.

## **1.4 Neurodevelopment in childhood**

Fetal growth impairment has been shown to be associated with a number of developmental impairments<sup>65,66</sup> and neurodevelopmental disorders<sup>49,67</sup>. Numerous large-scale follow-up studies, such as INCAP<sup>68</sup> and ALSPAC<sup>69</sup>, have suggested that fetal growth impairment is associated with significant deficits across a range of neurodevelopmental outcomes in childhood, including behaviour, cognition, language, motor, vision, hearing and sleep development<sup>1,70-75</sup>. An explanation of some of these domains, adapted from a recent review<sup>76</sup> is presented in Table 1.1.



**Table 1.1. Description of developmental domains and subdomains**

| Developmental domains | Description of domain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cognitive             | <p>Strategies and processes children develop to interpret and respond to their environment and experiences including; memory (ability to encode, retain and recall information over time) and attention (the ability to choose what to focus on for a sustained period).</p> <p>New born explores the world by mouthing objects; and later explores the world by imitating actions, manipulating objects and planning two-step strategies to get what he wants.</p> <p>From 2 years, children increase their use of language and start make-believe play.</p> <p>In children aged 3–5 years there is rapid development in information processing (the speed and fluency of response following stimuli), cognitive flexibility (the ability to make and change strategies as required and to simultaneously process multiple stimuli) and goal setting (the ability to plan strategies in a coherent and efficient order).</p> |
| Language              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Receptive             | Understanding of the spoken word and sentence structure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Expressive            | Spoken vocabulary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Motor                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Fine motor            | Ability to manipulate small objects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Gross motor           | Ability to walk, run and coordinate complex physical activities                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Social and emotional  | The ability to identify and understand one's own feelings and to accurately read and comprehend emotional states in others. Ability to regulate one's own emotion, to develop empathy for others, and to establish and maintain relationships                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Behaviour             | Collection of conceptual, social and practical skills that have been learned by people in order to function in their everyday live. Behavioural disturbance includes behavioural problems such as global attentional and hyperactivity difficulties, and oppositional and conduct problems.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Failure to reach optimal neurodevelopment is referred to as loss of developmental potential<sup>77</sup>. It is estimated that over 200 million children under the age of 5 years in LMICs are affected by losses in their developmental potential<sup>78</sup>, associated with a lower school achievement<sup>79</sup> and attainment<sup>80</sup>. Child neurodevelopment is important as it is associated with a range of outcomes later in life. A range of negative long-term outcomes have been associated with neurodevelopmental impairments, including poor educational outcomes, poor physical and mental health, financial problems, and substance dependence in adolescence and adulthood<sup>81,82</sup>.

In addition to impaired fetal growth, a number of proximal and distal maternal, and family factors, as well as intermediate factors during childhood have also been associated with neurodevelopment in childhood<sup>83</sup>. Of these, however, impaired fetal growth represents the earliest child-related factor (as opposed to maternal or social factors) which can indicate increased risk of neurodevelopmental impairment (Figure 1.6).

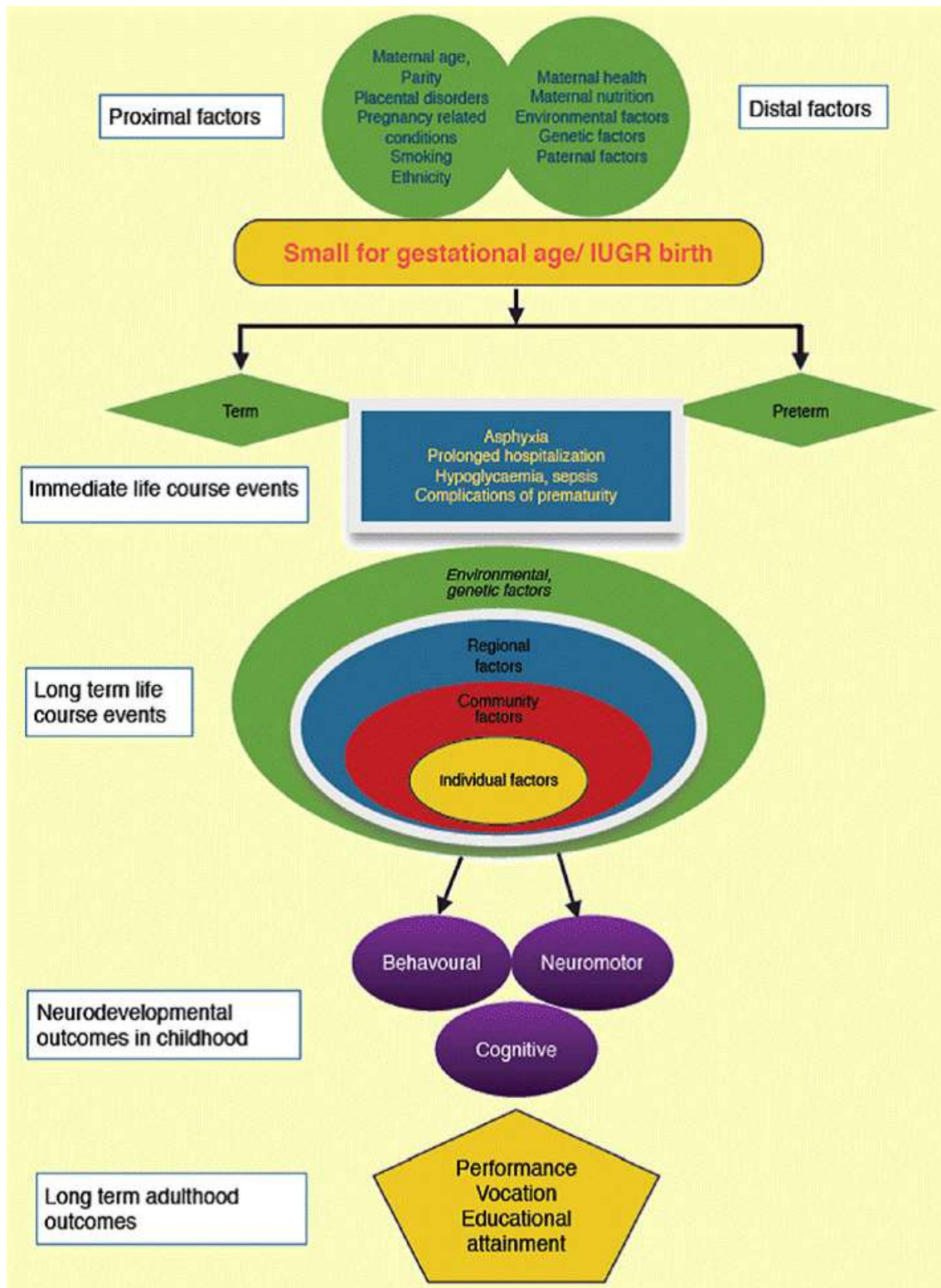


Figure 1.6. Contributing factors and long-term outcomes associated with childhood neurodevelopment<sup>83</sup>

### **1.4.1 Cognitive and attention development and function**

Two important and related domains of neurodevelopment which may be associated with fetal growth (and which will later be examined as the primary outcomes of interest in Chapters 5, 6 and 7 of this thesis) are cognitive development and attention. Cognitive abilities refer to the processes used to interpret and respond to the environment and experiences. Cognitive abilities are observable from birth, where the neonate explores the world by mouthing objects. Following the neonatal period this exploration progresses to imitating actions, manipulating objects and planning two-step strategies. In children aged 3–5 years there is rapid development in information processing (the speed and fluency of response, following stimuli), cognitive flexibility (the ability to make and change strategies as required and to simultaneously process multiple stimuli) and goal setting (the ability to plan strategies in a coherent and efficient order).

The period of cognitive development has been divided into three sequential stages: emerging (early stage of acquisition and not yet functional), developing (capacity is partially acquired but not fully functional), and established (ability fully mature)<sup>84</sup>. There is some debate as to when maturity is fully reached, however it is generally considered to continue into adolescence, and until early adulthood<sup>85</sup>. Cognitive assessments are usually conducted using objective tests of the child's abilities to achieve a set of goals. Further considerations of testing are discussed in Section 1.3.3.

A key neurodevelopmental function related to cognitive development is attention. Attention to salient features in the environment is a key component of learning and cognition<sup>86</sup>. Early attention development is guided by several underlying systems that emerge and function differently, at different points during development<sup>87</sup>. During the first year of life, four different functions of attention come online (alertness, spatial orienting, attention to object features and endogenous attention) and develop at separate points in time<sup>88</sup>. Attention development, during

the first 6 months of postnatal life, is predominantly controlled by exogenous factors (i.e. stimulus characteristics and novelty)<sup>89</sup>. As infants approach 12 months of age, there appears to be a 'transition', such that endogenous control of attention (i.e. top-down, self-regulated control) increases<sup>87,90</sup>, and continues to develop into childhood<sup>91</sup>.

Endogenous attention encapsulates easily observable, behavioural constructs of attention, including attention span, distractibility and persistence. It is these observable attention difficulties that are identified in parent-report measures, and have also been shown to be associated with a diagnosis of attention deficit hyperactivity disorder (ADHD). A systematic review by Danckaerts et al. (2010)<sup>92</sup> showed that ADHD has significant effects on quality of life according to parental report. As such, assessing attention problems in childhood is important due to (a) the potential effect on learning and the relation to cognition, and (b) the potential for more severe clinical-level problems, such as ADHD.

#### **1.4.2 Neurobiology of normal neurodevelopment**

A potential link between impaired fetal growth and neurodevelopmental outcomes may be the disturbance of physiological processes underpinning neurodevelopment. Neurodevelopmental domains develop following different trajectories during childhood (Figure 1.7). A brief description of normal neural developmental processes will be provided below, followed by the manner in which these processes may be disturbed in growth impaired fetus.

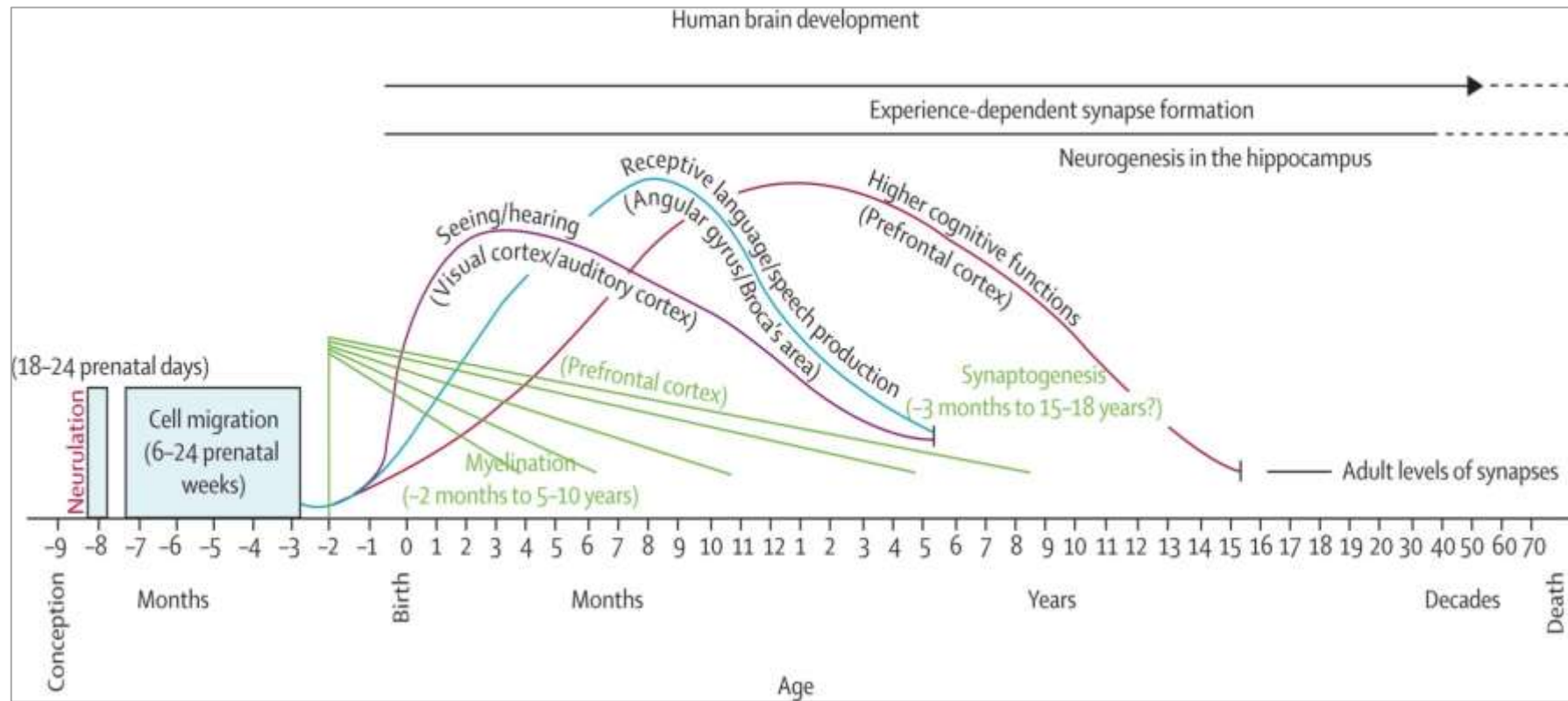


Figure 1.7. Trajectories of development of different neurodevelopmental domains<sup>93</sup>

In normally developing fetuses, neural development begins in the first weeks post-conception, beginning with proliferation of radial glia and neurons (Figure 1.8). During early development, neurons proliferate and migrate, reaching their final destination at approximately the 16<sup>th</sup> fetal week, after which they arborize and attempt to establish appropriate connections<sup>94</sup>. During the second half of gestation, profound changes in neural organisation occur in which critical connections are established, and important neural tracts become myelinated<sup>95</sup>. Further dramatic morphological rearrangement occurs in the period immediately before birth, in the process of apoptosis<sup>96</sup>, which is functionally hypothesised to increase the efficiency of synaptic transmission<sup>97,98</sup>. In addition to these global developments, particular neural regions also develop at different periods, with late-developing structures, such as the cortex and hippocampus developing primarily in the third trimester<sup>99,100</sup>. In human infants, the primary brain growth spurt begins in mid-pregnancy and continues until approximately 24 months postnatal age<sup>101</sup>.

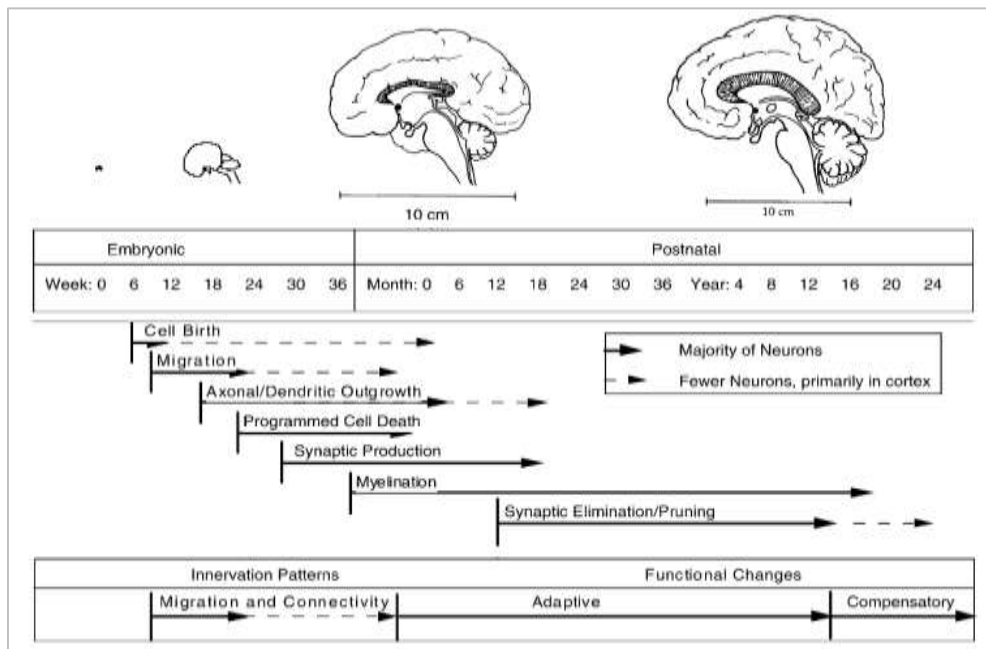


**Figure 1.8. The stages of brain development<sup>102</sup>**

### **1.4.3 Effect of impaired fetal growth on neural development**

The potential neural disturbances that mediate the relationship between impaired fetal growth and neurodevelopmental outcomes have been the subject of a great deal of recent research. Insult to the fetal brain during development, even of small magnitude, can result in disturbance of neural developmental processes<sup>103</sup>. Fetal growth impairment has been associated with a specific neurostructural differences in cortical volume, particularly a reduction in absolute grey matter<sup>104,105</sup>. Alterations in grey and white matter distribution, which are present into adulthood<sup>106</sup>, are proposed to reflect abnormal connectivity<sup>107</sup>. This abnormal connectivity may arise from a number of regressive and progressive events occurring simultaneously throughout development. Such changes have been identified in animal models of fetal growth impairment in both rodents and sheep. These models have demonstrated fetal growth impairment to be associated with a reduction in cell number and size, related to an overall reduction in brain weight<sup>108</sup>, as well as a decrease in axon myelination<sup>109</sup>. Furthermore, fetal growth impairment has also been identified to lead to a decrease in dendritic arborization<sup>110,111</sup>, synaptogenesis<sup>112</sup> and neurotransmitter availability<sup>113,114</sup>, in both human and animal studies.

There may also be specific neural changes arising from FGR. Increased perfusion of the fetal brain has been identified to lead to alterations in regional cerebral hemodynamics, specifically a decrease in blood flow to the frontal areas, involved in executive functions such as cognitive control, in favour of the basal ganglia, a set of cranial nuclei involved in the regulation of motor control<sup>115</sup>. Regional neural changes may be the underlying factor leading to impaired neurodevelopmental outcomes of children with fetal growth impairment<sup>75,116</sup>.

This suggests that there may be a characteristic pattern of neurodevelopmental deficits in children with fetal growth impairment<sup>105</sup>, reflecting the way in which altered cerebral circulation affects the developing brain in a regionally-specific manner. Whether such a pattern



exists, however, remains a source of debate<sup>117,118</sup>, and will be examined further in the systematic review (Chapter 2) of this thesis.

#### **1.4.4 Neurodevelopmental assessments: screening tools and in-depth assessments**

In order to examine the effects of fetal growth on neurodevelopment, good quality assessments are required. Neurodevelopmental assessments test the subject's ability to carry out a number of tasks of varying difficulties, and result in a neurodevelopmental score across different domains. There are various methods of neurodevelopmental assessment, including direct assessment by a trained assessor, completion of a questionnaire by parent and naturalistic observations of the subject in an environment in which they are comfortable. Broadly, neurodevelopmental assessments can be divided into screening and in-depth tests<sup>119</sup>. Screening tools use a limited number of items and are thus quick to administer. The selection of assessment items in screening tests rely on some pre-determined level of ability, usually derived from existing knowledge of age-related developmental competencies. Screening tools are designed to identify children who may be in need of further in-depth neurodevelopmental testing. As stand-alone assessments however, screening tools have poor utility in identifying nuanced delays that may have significant impact on subsequent development<sup>76</sup>. In-depth assessments take longer to administer than screening tools and require highly specialised training of assessors. They generally allow administration of items above or below the subject's age bracket to account for potential floor and ceiling effects. The advantage of such assessments however, is that they provide a nuanced picture of neurodevelopmental strengths and weaknesses.

##### **1.4.4.1 Key factors relevant to neurodevelopmental assessments**

Assessing neurodevelopment is a complex task that requires consideration of numerous critical factors, such as the timing (age) of assessment, and cultural considerations. Age of assessment is important, as any neurodevelopmental assessment provides only a snapshot of

development at that point in time. Before 2 years of age, indices of neurodevelopment have been shown to have relatively low predictive validity for long-term outcomes<sup>120</sup>. This may be partly due to the restricted capacities of infants to express their cognitive abilities<sup>121</sup> (e.g. immature verbal and sensorimotor systems), and the high level of plasticity of ongoing neural development processes<sup>101</sup>. From 2 years however, the predictive validity of neurodevelopmental assessment increases<sup>120</sup>. The benefit of conducting neurodevelopmental assessments at the earliest possible age at which there is reasonable predictive validity (i.e. 2 years of age) is that there is less intervening postnatal time, and therefore reduced influence of intervening factors that may potentially confounding the associations of interest.

As children get older, however, assessors are able to conduct more substantial neurodevelopmental testing. Owing to increases in the range and clarity of a child's response capabilities, assessments of preschool and school-aged children can generate a more differentiated picture of developmental strengths and weaknesses. As such, functional impairment that may not have been identified in earlier assessments may become apparent through more sophisticated assessments at later developmental stages<sup>122</sup>. Furthermore, due to increased social maturity, autonomic stability and attentional capacities; neurodevelopmental assessment sessions in older children can be of greater duration, and thus assess a wider range of abilities within a single testing session<sup>121</sup>. The current thesis includes neurodevelopmental assessments of children across developmental ages within limited bounds, from 2 years to 6 years.

Cultural appropriateness is another important consideration of neurodevelopmental assessments. It is important when conducting neurodevelopmental assessments that the tests and language used are appropriate for the culture of the population in which the test is being conducted. Neurodevelopmental assessments that are used cross-culturally but are not assessed for cultural appropriateness risk confounding results with cultural familiarity<sup>123</sup>. For

example, a child that is not accustomed to the use of cutlery in the home may struggle on at item requiring the use of a spoon to feed a doll. This child is not neurodevelopmentally incapable of performing the task, but is culturally unfamiliar with the use of the item involved. It is thus important that neurodevelopmental assessments are 1) conducted in a language that the child knows and speaks; and 2) either have been developed to be free from cultural bias, have been developed specifically for use in that population, or have been validated for use in that population.

## **1.5 Sex differences in the association between fetal growth and neurodevelopment**

There has been very little research into potential sex differences in the association between fetal growth and neurodevelopmental outcomes. Need for research in this field is particularly important given sex-specific differences have been identified in most facets of human structure and function, including perinatal growth, susceptibility to disease, neonatal survival rates<sup>124-126</sup>, and the prevalence and severity of developmental disorders<sup>127,128</sup>. The key findings from this research that are of relevance to this thesis will be introduced below.

### **1.5.1 Sex differences in fetal development and the prevalence of neurodevelopmental disorders in the general population**

Neurodevelopmental disorders (disorders with childhood onset) such as ADHD, learning disabilities, developmental language disorders, and autism spectrum disorder, show a marked male preponderance<sup>128</sup>. Only relatively recently, however, has research started to examine sex differences in the biology, development, antecedents, correlates and outcomes associated with psychopathology<sup>128</sup>.

The male preponderance of developmental impairments in childhood have been suggested to be related to sexual dimorphism in neural development and the development and function of the hypothalamic-pituitary-adrenal (HPA) axis<sup>128</sup>. Sexual dimorphism in neural

development begins in utero, when the activity of sex hormones (androgens, such as testosterone, for males and estrogen for females), masculinizes or feminizes the brains and bodies of fetuses.

Sex hormones have been shown to organise neuronal circuitry in the size of neural regions, synaptic connections, neurotransmitter concentrations and their activity<sup>129</sup>. Overall, the developing male brain is approximately 10% larger than the female brain<sup>130</sup>. After correcting for brain volume differences, regional differences have also been identified, with a smaller caudate, and a larger globus pallidus in males<sup>131</sup>. Furthermore, the rate of development has been shown to have regionally-specific differences between males and females<sup>132</sup>. The rate of development of the frontal cortex, caudate, and temporal lobes in females has been shown to be considerably faster than in boys, by as much as 20 months<sup>128</sup>.

There have also been sex differences identified in the development of the hippocampus. Hippocampal formation volume has been shown to increase with age for females, but not for males<sup>133</sup>. This may be consistent with the distribution of sex hormone in the hippocampus, which has a predominance of estrogen receptors<sup>134</sup>. Prenatal testosterone exposure has been suggested to account for overall slower biological and physical maturation, and greater disinhibition in males than females<sup>135</sup>. This delayed maturation may create a specific risk for externalising behavioural problems in males<sup>128</sup>.

Development and function of the HPA axis has also been shown to differ between the sexes. The HPA axis, which controls a portion of the stress response, consists of three major endocrine glands, the hypothalamus, anterior pituitary and the adrenal cortex. It produces glucocorticoid hormones, including cortisol. Development and function of the HPA axis is affected by androgens and estrogens (Figure 1.9). Sex differences in HPA axis function have been identified in both human and animal studies, as early as the neonatal period<sup>136,137</sup>. Furthermore, a study of preschool children (aged 5) found a consistently higher level of

salivary cortisol in females<sup>138</sup>. Generally, however, the most consistent findings have been in adults, where females have been shown to have a higher stress-induced secretion of corticosterone (a glucocorticoid) compared to males<sup>139</sup>.

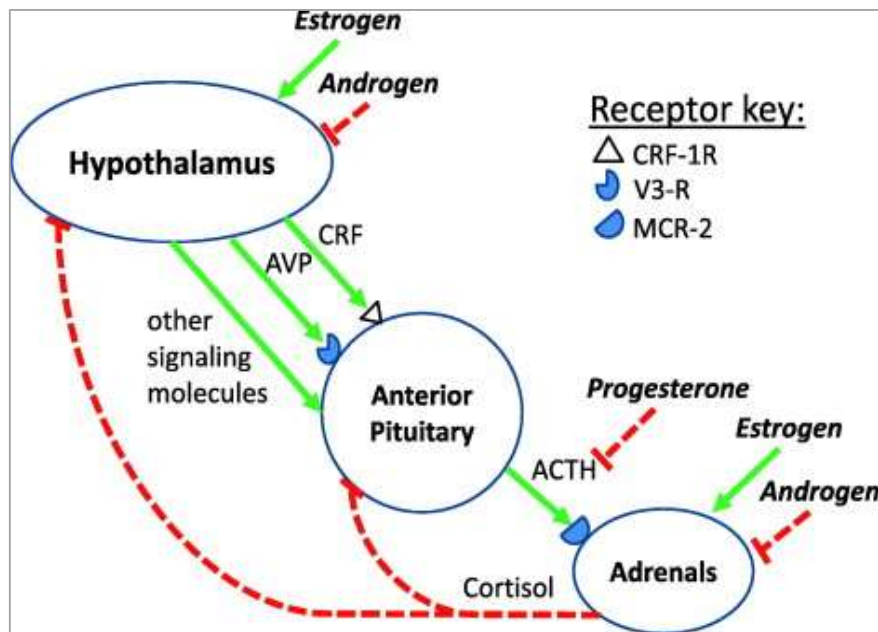


**Figure 1.9. Overview of the HPA axis and the effect of sex steroids.** Stimulatory inputs are depicted in green arrows and inhibitory signals in dashed red lines. Initial signals from the hypothalamic nuclei descend via the portal blood stream to the anterior pituitary and stimulate production and secretion of ACTH. In turn, ACTH causes production of cortisol from the zona fasciculata. Negative feedback from cortisol is exerted at the levels of the anterior pituitary corticotrophs and hypothalamic nuclei. ACTH: Adrenocorticotrophic hormone; CRF: Corticotrophin Releasing Factor; AVP: Vasopressin; CRF-1R: Corticotrophin Releasing Factor Receptor 1; V3-R: Vasopressin Receptor 3; MCR-2: Melanocortin Receptor 2139

Functional differences in the HPA axis have been suggested as the biological mechanism underpinning sex differences in a number of psychopathologies<sup>128</sup>. Antisocial behaviour in males has been linked to low responsiveness in the HPA axis<sup>140</sup>, and low cortisol has been shown to increase the association between testosterone and aggressive behaviours<sup>141</sup>. Furthermore,

glucocorticoids have been shown to alter affective and cognitive behaviours, with particular effects identified in attentional processes, such as vigilance<sup>142</sup>. Normal vigilance function has been shown to be crucial for memory formation<sup>143</sup>, and glucocorticoid deficiency has been shown to impair hippocampal-dependent memory formation<sup>144</sup>. As such, sexual dimorphism in the development and function of the HPA axis may suggest sex-specific effects in the associations between fetal development (e.g. growth) and neurodevelopmental outcomes in childhood.

### **1.5.2 Potential sex differences in associations between fetal growth and neurodevelopment: theoretical models**

As well as examining sex differences in neural development and neurodevelopmental disorders independently, more research is beginning to examine the dynamic interactions between these factors, such as differences between sexes in models of diathesis-stress<sup>145</sup>, and the associated neural mechanisms<sup>146</sup>.

Eme's gender paradox of neurodevelopmental disorders<sup>127</sup> refers to the observation that the sex less frequently affected by a neurodevelopmental disorder (i.e. girls with attention problems), are more likely to be more severely afflicted (i.e. have a defective genetic and/or environmental background such as prenatal growth disturbance). Two opposing mechanisms are suggested for this paradoxical observation - the polygenetic multiple-threshold model and the constitutional variability model. The polygenetic multiple-threshold model suggests that disorders are caused by a combination of multiple risk factors. Together, these risk factors determine individual vulnerability (or risk) of a disorder. Risk beyond a certain threshold will precipitate the disorder. The polygenetic multiple-threshold model suggests that this threshold differs between the two sexes, with a higher threshold in females. To reach this higher threshold, females require a greater number of risk factors to develop the disorder. Females presenting

with the disorder will thus have more risk factors in their background than males, indicated by greater defective genetic or environmental background.

The constitutional variability model draws on evidence that males are developmentally less mature than females and suggests that males are more susceptible to damage than females (due to systems immaturity). For females to cross the threshold into disorder, there needs to be an increased level of pathology, such as neural damage, as greater maturity provides some degree of neuroprotection. Although these models both converge on the idea that females presenting with neurodevelopmental impairment are more likely to have increased defective genetic or environmental backgrounds compared to males, they are opposed in their conceptualization of sex-differences in mechanisms of vulnerability (the former assumes equal vulnerability but different threshold whereas the latter assumes differential vulnerability). This thesis aims to test whether there is a sex-difference in the vulnerability associated with fetal growth impairment for childhood neurodevelopmental, which may help identify which model is superior.

Both models of Eme's gender paradox suggest that there may be a stronger association between risk factors (e.g. fetal growth impairment) and neurodevelopmental outcomes in females. The limited research into sex differences in the association between fetal growth and neurodevelopment has shown inconsistent results, however. Whereas some studies have identified growth restricted or preterm females to have a higher risk of neurodevelopmental impairment<sup>147,148</sup>, others have identified males as having a higher risk<sup>149-151</sup>, or have identified no difference between sexes<sup>152,153</sup>. Further research is needed to determine whether sex differences exist in the association between impaired fetal growth and neurodevelopment in childhood. This will be examined in Chapter 7.

## **1.6 The confounding effects of preterm birth**

A large proportion of neonates with fetal growth impairment also have comorbid preterm delivery<sup>154</sup>, and the effect of these insults combined confers a substantial risk for neurodevelopmental deficits<sup>155,156</sup>. Preterm birth (<37<sup>+0</sup> weeks GA) is the leading cause of perinatal morbidity and mortality worldwide<sup>1</sup>, above fetal growth impairment, and is also associated with an increased risk for cognitive<sup>157</sup>, sensory<sup>74</sup> and behavioural<sup>158</sup> disabilities. The manner in which fetal growth impairment and preterm birth interact in augmenting the risk of neurodevelopmental deficits however is not fully understood, and remains a source of debate<sup>159</sup>. Some studies have suggested that fetal growth impairment confers an *additional* risk to system immaturity, and that fetal growth impairment and preterm birth interact in an additive manner<sup>56,160</sup>. Others have suggested that the timing of delivery moderates the association between fetal growth impairment and neurodevelopmental deficits, such that early preterm birth might have an overriding negative effect on neurodevelopment<sup>161,162</sup>, but in cases of late preterm birth, fetal growth impairment may confer added risk.

One of the main difficulties in disentangling the risks contributed by fetal growth impairment and preterm birth to neurodevelopment, lies in the fact that many large-scale studies have often combined term and preterm infants in a single cohort, or have not statistically adjusted models for GA at birth. As such, ideal studies in this field should account for GA at birth, either by statistical adjustment for GA at birth or by dividing groups based on timing of delivery<sup>83</sup>. The current thesis draws on both techniques, primarily using statistical adjustment (Chapters 5, 6 and 7), but also separating groups when statistical adjustment is not possible (Chapter 2).

## **1.7 The importance of studying populations from low- and middle-income countries**

As previously stated, the majority of research on the neurodevelopmental effects of fetal growth impairment has been conducted in HICs, despite a much higher prevalence of



perinatal problems<sup>163</sup> and perinatal mortality<sup>164</sup> in LMICs (Figure 1.10; Figure 1.11). The rate of LBW is believed to be approximately six times higher in LICs, compared to HICs<sup>165</sup>. Furthermore, fetal growth impairment accounts for a greater proportion of LBW infants in developing countries than in developed countries, accounting for approximately 23.8% of all births, compared to approximately 10% in developing countries<sup>166</sup>.

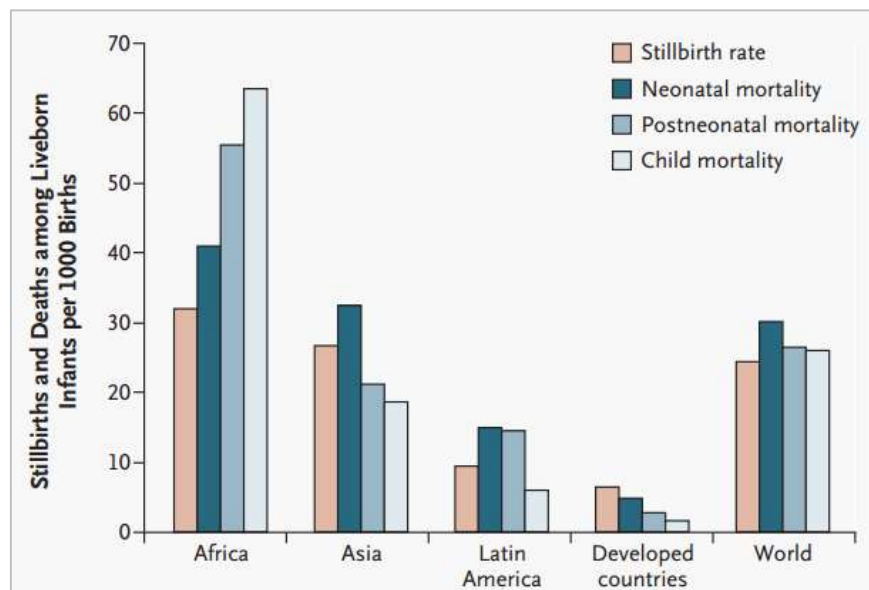


**Figure 1.10. Child mortality rates and rates of stillbirth in 2000.among liveborn infants per 1000 births Taken from Zupan (2005)<sup>164</sup>**



**Figure 1.11. Infant mortality rate (probability of dying between birth and age 1 year per 1000 live births), 2013. Data from UNICEF (2014)<sup>167</sup>.**

As well as differences in prevalence, there may also be differences between HICs and LMICs in the factors contributing to fetal growth impairment. The factors which determine differences in fetal growth impairment within populations are not necessarily the same those which operate between populations<sup>168</sup>. HICs have been shown to differ markedly to LMICs, with systematic differences in socio-demographic, maternal and perinatal health structures between these populations<sup>169</sup>. Variation in the prevalence of stunting and wasting across countries may thus arise from a number of social, demographic and economic differences at national level. Such national-level factors contributing to the higher rate of fetal growth impairment in LMICs, may include poorly treated maternal complications, maternal undernutrition, inadequate and/or under-resourced neonatal care and infections<sup>8,170</sup>.

The prevalence of serious neurodevelopmental impairment also varies widely across geographical locations, with a prevalence of 2.0–4.5 per 1000 children reported from HICs compared to 5.3–24.3 per 1000 children in LMICs<sup>171</sup> (Figure 1.12). These estimates are suggested to include only the proverbial tip of the neurodevelopment iceberg, with estimates of the

prevalence of mild neurodevelopmental impairment believed to be much higher<sup>172</sup>. Children from LMICs have been reported to have a higher prevalence of mild neurodevelopmental impairment compared to those in HICs, with a higher prevalence of impairments in cognitive, physical and social development<sup>173,174</sup>.

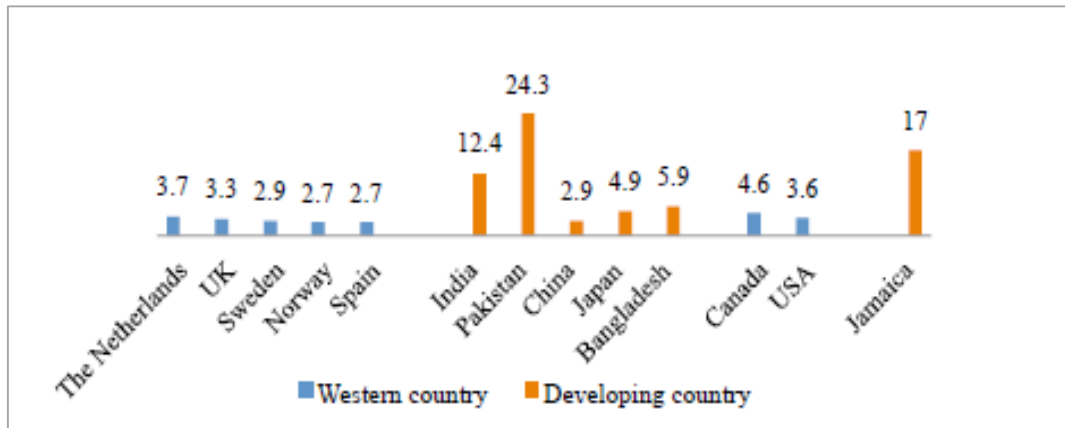


**Figure 1.12. Prevalence of serious neurodevelopmental impairment per 1000 children in selected high-, and middle- and low-income countries. Taken from Durkin (2008)<sup>171</sup>.**

Studies of children in LMICs have shown that early cognitive development predicts later school outcomes, after accounting for wealth, maternal education, child sex and age<sup>175-177</sup>. In developing countries, an estimated 99 million primary-school aged children are not enrolled in school, and of those enrolled, only 78% complete primary school<sup>178</sup>. The highest rate of failure to complete primary school is in south Asia and sub-Saharan Africa, with only approximately 50% enrolled in secondary schools<sup>77</sup>. Furthermore, children in LMICs have been shown to have much lower achievement levels than those in HICs in the same grade<sup>179</sup>. As such, neurodevelopmental impairment causes a major socioeconomic burden, particularly in LMICs<sup>180</sup>, and plays an important part in the intergenerational transfer of disadvantage and poverty<sup>77</sup>. This has been shown to have profound consequences for the welfare and productivity of entire societies<sup>181</sup>.

One reason for the paucity of research in LMIC samples is the relative lack of culturally appropriate, validated tools and trained professionals to carry out neurodevelopmental assessments, which often require substantial resources, infrastructure and specialist healthcare professionals<sup>182</sup>. Most assessments of neurodevelopment in childhood require specialized personnel and sophisticated infrastructure/equipment, which drastically limits the scalability of neurodevelopmental assessments for use in large populations. The INTERGROWTH-21<sup>st</sup> neurodevelopment assessment (INTER-NDA) has been designed to bridge this gap in the universal early childhood assessments<sup>183</sup>. A validation study of the INTER-NDA as an assessment of child neurodevelopment is reported in Chapter 4.

One method to examine the impact of different confounding structures between LMICs and HICs, is to compare LMIC and HIC samples that have been selected (using pre-determined criteria), to reduce the variation introduced through confounding. An example of such a study is the INTERGROWTH-21<sup>st</sup> Project from which low-risk samples from LMICs and HICs can be compared on the association between fetal growth impairment and neurodevelopment. This allows the examination of the association between fetal growth impairment and neurodevelopment when potential confounding effects have been held constant. Such cohorts may help provide insight into the extent to which confounding structures moderate the association between fetal growth impairment and neurodevelopment. This method of comparison is conducted in Chapter 6 (Study I) of this thesis, comparing low-risk samples from LMIC and HIC sites of the INTERGROWTH-21<sup>st</sup> Project.

## **1.8 Gaps in the literature**

To draw together the points raised in this introductory chapter, whilst there has been some research into the effects of fetal growth impairment on neurodevelopment in childhood, there are still many questions which remain unanswered. Firstly, research on fetal growth impairment has overwhelmingly relied on BW indices alone, which cannot provide information

about the fetal growth impairment phenotype. As such, there is no clear understanding of the effect of fetal growth impairment on childhood neurodevelopment. Recent research has identified differences between stunting and wasting growth phenotypes on short-term outcomes<sup>25</sup>, however there has yet to be an examination of whether there may be differences in longer-term neurodevelopmental effects.

Secondly, very few studies have examined potential differences between sexes in the effect of impaired fetal growth on neurodevelopment. Research has suggested that male and female fetuses may have differential vulnerability to intrauterine insult, however the research on sex differences in long-term neurodevelopmental effects, to date, has been inconclusive.

Finally, research in this field has largely been carried out in samples from HICs, which have a lower prevalence of stunting, wasting and neurodevelopmental impairment in childhood, as well as differences in confounding structures (such as maternal health and obstetric care), compared to LMICs. This over-reliance on data from HICs is largely due to the resources, infrastructure and specialised health professionals required to conduct neurodevelopmental assessments. As such, there is a pressing need for research into whether the association between fetal growth impairment and neurodevelopment differ between HICs and LMICs.

## **1.9 Aims of the research**

The overall objective of this research is to compare the association between impaired fetal growth, using a range of anthropometric indices measured at birth, and attention and cognitive outcomes in childhood. This objective is divided into five specific sub-aims:

- I. Examine the overall association between fetal growth impairment and neurodevelopment in childhood, by conducting a systematic review of the literature using a stringent definition of fetal growth impairment.

- II. Conduct a validation of the INTER-NDA, a neurodevelopmental assessment tool to assess neurodevelopment at age 2, against a current 'gold standard' infant neurodevelopmental assessment.
- III. Examine whether there are differences in associations between birth indices of impaired fetal growth (including BW, stunting, wasting and asymmetry at birth) and attention and cognitive development in childhood.
- IV. Examine whether the associations between birth indices of impaired fetal growth and attention and cognitive development differ between high-, middle- and low-income countries.
- V. Examine whether the associations between birth indices of impaired fetal growth and attention and cognitive development are moderated by sex.

### **1.9.1 Research hypotheses**

Based on previous research, and pertaining to each of the above aims, it is hypothesised that:

- I. Fetal growth impairment will be associated with neurodevelopmental deficits in childhood.
- II. The INTER-NDA will be a valid tool for assessing neurodevelopment in early childhood.
- III. Stunting and wasting at birth will be more strongly associated with attention and cognitive impairment in childhood than LBW, and stunting will be more strongly associated with impairment than wasting.
- IV. Associations between anthropometric indices at birth (LBW, stunting, wasting and asymmetry) and poor attention and cognitive outcomes will be stronger in LMICs than in HICs.
- V. Females will show stronger associations between impaired fetal growth and attention and cognitive impairment than males.

### **1.10 Structure of the thesis**

The thesis includes eight chapters in total. Each of the five results chapters (Chapters 2, 4, 5, 6, 7) addresses a separate aim, addressed in order from Aim I to V. A General Methodology (Chapter 3) and a General Discussion chapter (Chapter 8) are also included.

A specific breakdown of each of the chapters is as follows: Chapter 1 is a general introduction, laying out the background information required to frame the research questions. Chapter 2 is a systematic review of the literature, addressing the current lack of consensus on the effect of fetal growth impairment on neurodevelopment in childhood (Aim I). Chapter 3 covers the general methodology and assessment tools used. Chapter 4 is a validation study of the INTER-NDA, against the current gold standard of infant neurodevelopmental assessment, the Bayley Scales of Infant Development (Aim II). Chapter 5 is an analysis of the associations between the different growth phenotypes at birth and attention and cognitive development in childhood (Aim III). Chapter 6 is an analysis of differences between high-, middle- and low-income countries (Aim IV) and Chapter 7 is an analysis of sex differences in the associations between impaired fetal growth and attention and cognitive development in childhood (Aim V). Finally, the results are discussed in the context of existing research, the strengths and limitations of the research are presented, and the future clinical and research implications are included in the general discussion chapter (Chapter 8). A diagram of the thesis structure is presented in Figure 1.13.

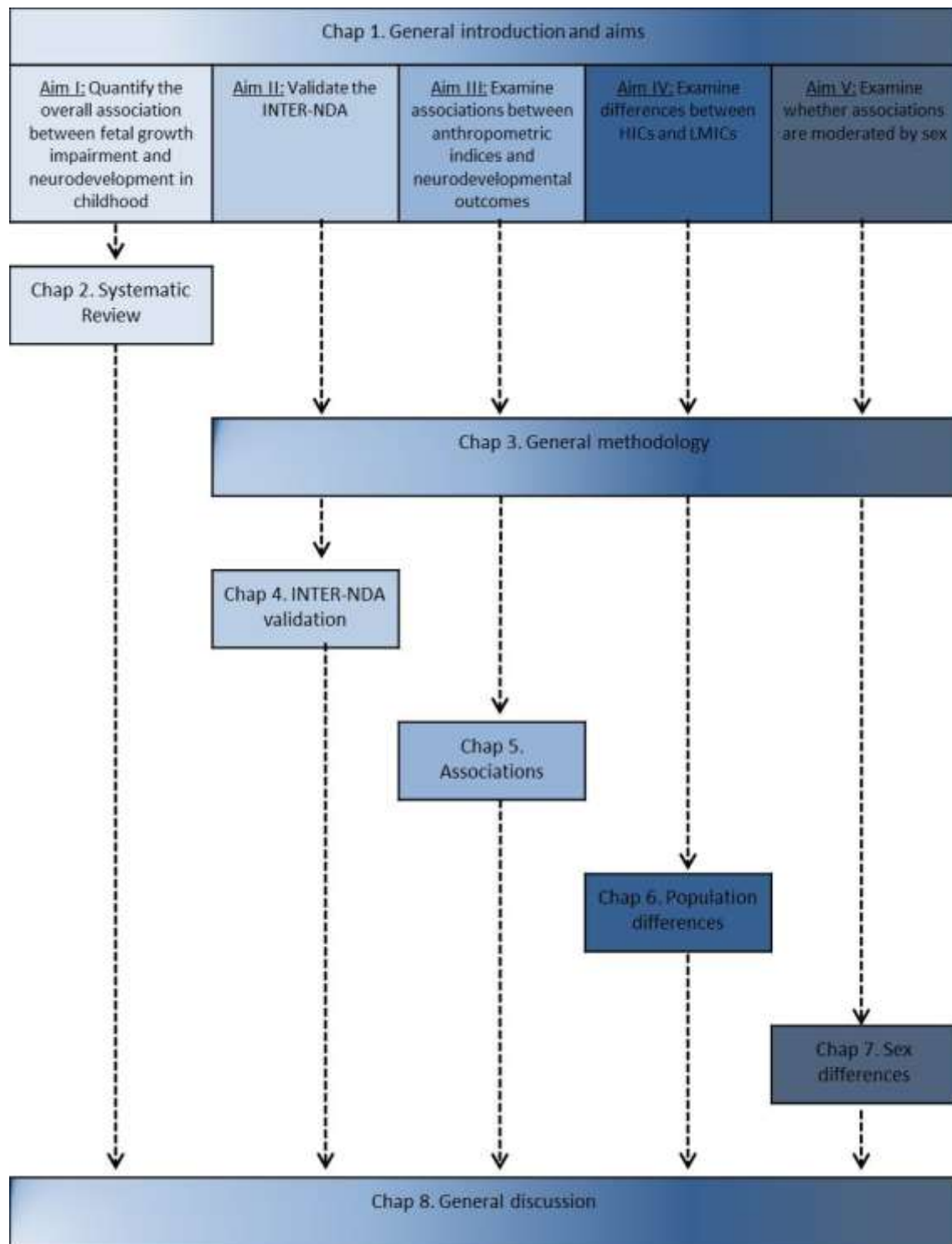


Figure 1.13. Graphical representation of the structure of the thesis. Arrows represent the way in which each chapter addresses the aims detailed in the introduction.



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## **2 Systematic Review: The effect of impaired fetal growth on neurodevelopment in childhood.**

### **Chapter outline**

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## 2.1 Introduction

The aim of this chapter is to address the first aim of the thesis, to examine the association between impaired fetal growth and neurodevelopment in childhood, by conducting a systematic review of the literature. A systematic review of the existing literature is required to: 1) quantify the overall effect of impaired fetal growth on neurodevelopment (using stringent criteria for the identification of growth impairment to reduce variation in measurement methodologies); 2) identify which neurodevelopmental domains may be more affected than others; and 3) examine whether the phenotype of growth impairment (i.e. stunting or wasting) may have differential effects on the neurodevelopmental outcome. This systematic review will help determine which neurodevelopmental domain to focus on for the rest of the thesis.

To recap from Chapter 1, the literature surrounding the effect of impaired fetal growth on neurodevelopmental outcomes has been relatively inconsistent. Firstly, there is a large amount of heterogeneity between studies, in both growth assessments used and outcome measures. Secondly, there has been an over-reliance on birth weight (BW) alone as an index of fetal growth impairment. Thirdly, most studies have aggregated across neurodevelopmental domains, and there have been few studies comparing effects across neurodevelopmental domains. Finally, no studies have examined which growth impairment phenotype (i.e. stunting or wasting) is more strongly associated with neurodevelopmental impairment.

Despite the utility of anthropometric indices at birth as an indicator of fetal growth and for characterising the phenotype of growth restriction (e.g. fetal stunting compared to wasting)<sup>1</sup>, the optimal method of identifying restricted growth uses in utero measures, such as serial fetal biometry or Doppler velocimetry, confirmed with birth anthropometric indices of restricted growth. Fetal biometry and Doppler velocimetry allow the clinical deterioration associated with fetal growth impairment to be characterised<sup>2</sup>.

Serial ultrasound can provide a direct measure of prenatal growth dynamics. Serial fetal biometric assessments, such as measurements of biparietal diameter (BPD), occipito-frontal diameter, head circumference (HC), transverse abdominal diameter, antero-posterior abdominal diameter, abdominal circumference (AC), and/or femur length (FL), allow clinicians to identify the onset of fetal growth impairment and the rate of deteriorating growth more accurately<sup>3</sup>. Increasing the precision with which fetal growth patterns can be determined allows a more refined examination of the relationship between fetal growth impairment and neurodevelopmental outcome. Studies using this technique<sup>4-6</sup> have been able to examine nuances of the effect of fetal growth impairment, such as the timing of onset.

The haemodynamic adaption associated with progressive fetal growth impairment (fetal circulatory redistribution; FCR) can be identified using Doppler ultrasonography, which allows quantification of blood flow velocity in the fetoplacental circulatory system. In the presence of restricted fetal growth (corroborated by anthropometric indices at birth), Doppler ultrasonography provides a useful tool with which to differentiate the growth impaired fetus from that which is constitutionally small but normally grown<sup>7</sup>. Characteristic changes in the circulatory system in growth impaired fetuses have been identified in the blood flow velocity waveform of umbilical artery (UA), umbilical venous, uterine artery, ductus venosus, aortic artery, anterior cerebral artery and middle cerebral artery (MCA). Doppler evaluation is often carried out by using blood flow velocity to calculate the pulsatility index, which reflects the resistance to flow in the peripheral vasculature<sup>8</sup>. The most robust identifier of placental insufficiency is the elevation of the UA pulsatility index, which indicates the extent of placental dysfunction, and overall speed of deterioration in fetal growth impairment<sup>2</sup>. Additionally, an indicator of the vasodilatation of the cerebral circulation can be identified by a reduction in the MCA pulsatility index<sup>9</sup>. This represents a decrease in resistance to blood flow, and thus increased perfusion of the fetal brain<sup>10</sup>. Therefore FCR can be identified by an increase in the cerebroplacental ratio (also often referred to as the U/C ratio), that is, the ratio between the UA and MCA pulsatility indices<sup>11,12</sup>.

A meta-analysis of the use of Doppler to predict poor fetal growth showed that abnormal UA Doppler measurements were a strong predictor of poor fetal growth, defined by measurements of low birth weight (LBW) or small-for-gestational-age (SGA) at birth (positive likelihood ratio of 9.1 – 14.6)<sup>13</sup>. Abnormal Doppler indices have also been shown to be significantly associated with specific anthropometric indices of stunting (including low birth length<sup>14</sup> and head circumference<sup>15</sup>) and wasting (ponderal index<sup>14</sup>) measured at birth. Doppler velocimetry is also an important way to identify FCR, an underlying mechanism of asymmetric anthropometric measurements at birth. Research has shown an association between a raised U/C ratio and anthropometric indices of asymmetry (higher HC compared to other anthropometric parameters)<sup>16</sup>, potentially reflective of the preferential redistribution of blood flow to the brain<sup>17</sup>, at the cost of substrate availability in the liver and other downstream organs<sup>18</sup>.

To date, there have been no systematic reviews that have examined the neurodevelopmental effects of fetal growth impairment, using these more stringent identification methods, or that have disaggregated effects across neurodevelopmental domains. Furthermore, there have been no attempts to systematically identify any differences that may arise from different growth phenotypes. As such, the primary aim of this systematic review is to quantify the overall effect of fetal growth impairment, identified in utero and confirmed at birth, on neurodevelopment in childhood. The secondary aims are to 1) identify any differential effects of fetal growth impairment across neurodevelopmental domains; and 2) identify any differential effects of varied growth phenotypes (stunting and wasting compared to BW indices).

## **2.2 Methods**

### **2.2.1 Search strategy and selection criteria**

Studies examining the childhood neurodevelopmental outcomes of fetal growth impairment were identified using internet-based scientific and medical databases. Databases searched to identify published, peer-reviewed studies included Medline, Cumulative Index to

Nursing and Allied Health Literature (CINAHL), PsycInfo, and Scopus. For unpublished studies, theses and dissertations, the World Health Organisation Library and Dissertations & Theses A&I were also searched.

The search strategy clustered terms used to describe fetal growth impairment and maintained these terms in the search, whilst progressively refining the specificity of the associated outcome, in three separate searches. The initial search included “fetal growth impairment”, “foetal growth impairment”, “intrauterine growth impairment”, “fetal growth restriction”, “foetal growth restriction”, “intrauterine growth restriction”, “fetal growth retardation”, “foetal growth retardation”, “intrauterine growth retardation”, or “prenatal growth disorder” and “outcome” or “prognosis”. A second search was then conducted, which replaced “outcome” or “prognosis”, with “neurodevelopment” to specifically identify neurodevelopmental outcomes of fetal growth impairment. Finally, “neurodevelopment” was replaced with each of the outcomes of interest in turn, including “cognitive” or “cognition”, “language” or “verbal”, “hearing” or “auditory”, “vision” or “visual”, “behaviour”, “behavior” or “temperament”, “sleep”, and “motor”. This search strategy was exactly replicated in all searched databases. A complete description of the terms used in each database search is presented in Table S2.1 (Appendix I).

In addition, a process of ‘proactive searching’ was carried out, in which a list of international research groups known to be conducting research in this field, was compiled and agreed upon. The heads of each of these groups were approached, and requests were made for any data, published or unpublished, that may be useful for the current review. This ensured that all steps were taken to compile the full amount of existing research in this field, and that no unpublished data was neglected in the search process.

The search period was limited to studies published between 1<sup>st</sup> January 1970 and 31<sup>st</sup> December 2012, as availability of reliable ultrasound in pregnancy would have been unlikely prior to this period, leading to unclear in utero identification of growth impairment. The database search

was supplemented with a manual search of reference lists of included articles, as well as key review papers, to further locate any studies that may not have been detected through the database search. No language restrictions were imposed.

Only studies with objective in utero identification of growth were included, to ensure that those babies defined as such were subject to growth impairment during the prenatal period. Acceptable methods of in utero identification of growth impairment included ultrasound biometry<sup>19</sup> (including ultrasonographic measures of biparietal diameter, occipito-frontal diameter, head circumference, transverse abdominal diameter, antero-posterior abdominal diameter, abdominal circumference, and/or femur length), and Doppler velocimetry<sup>20</sup> (including umbilical cord artery, umbilical cord venous, uterine artery, ductus venosus, aortic, and anterior and middle cerebral artery Doppler). Use of Clinical Assessment of Nutritional Status (CANS) score, amniotic fluid volume, abdominal palpitation, and symphysis-fundal height were not accepted as reliable measures of growth impairment, due to the lack of methodological validity and reliability of these methods (Figure 2.1).

In addition to clear identification of fetal growth impairment, strict inclusion criteria were also imposed on the methodology used at follow-up in the studies. The follow-up assessment must have been conducted after the neonatal period (4 weeks post-birth), but during childhood (no later than 12 years of age). These limits were determined due to the potentially decreased predictive validity of assessments conducted prior to 4 weeks post-birth, and the potential confounding effect of neurobiological changes associated with puberty. A trained clinician or researcher must have administered tests. The assessment must have been standardised, and have demonstrated reliability and validity. In the case of modified assessments, tests must have been validated against a standardised test. Parental report assessments were considered acceptable if they had been standardised, with demonstrated reliability and validity. Parental reports were not accepted in the domains of auditory and visual function however, as there is some evidence to suggest that whilst

parental and professional estimates of these disturbances may be highly correlated, there is often systematic difference in estimates<sup>21,22</sup>. Neurological examination was deemed acceptable only if the following three criteria were met: assessment conducted by a trained physician, adherence to a clear assessment protocol, and a high level of inter-rater reliability (>.80).

As such, studies were excluded if they did not demonstrate clear identification of fetal growth impairment, or appropriate follow-up methodology. Furthermore, presence of chromosomal disorders or congenital anomalies leading to fetal growth impairment were excluded, as were review papers, conference proceedings, and case studies, as the inclusion of case studies risks biasing the results of the systematic review.

**Inclusion criteria:**

- Stringent identification of fetal growth impairment in utero
  - ultrasound biometry: including ultrasonographic measures of biparietal diameter, occipito-frontal diameter, head circumference, transverse abdominal diameter, antero-posterior abdominal diameter, abdominal circumference, and/or femur length; AND/OR
  - Doppler velocimetry: including umbilical cord artery, umbilical cord venous, uterine artery, ductus venosus, aortic, and anterior and middle cerebral artery Doppler
- Fetal growth impairment identification confirmed by anthropometry at birth
- Follow-up period between 4 weeks post-birth and 12 years of age
- Follow-up carried out by trained clinician or researcher
- Standardized follow-up assessment with demonstrated validity and reliability

**Exclusion criteria:**

- Unclear identification of fetal growth impairment
- Inappropriate follow-up methodology
- Inclusion of subjects with chromosomal disorders or congenital anomalies
- Review papers
- Conference proceedings
- Case studies

**Figure 2.1. Inclusion and exclusion criteria for data included in the systematic review**



Initially, all titles of the studies identified in the search process, were systematically examined to exclude studies and papers not relevant to this review. The online abstracts of those not excluded were then reviewed with reference to the predefined inclusion/exclusion criteria, and further exclusions were made. The full text of the remaining studies were then scrutinised, and those fulfilling the above criteria were included in the final analysis.

### **2.2.2 Data extraction and quality assessment**

Data was organised into seven neurodevelopmental outcome domains, i.e. cognitive, language, motor, hearing, vision, behaviour and sleep. In the case of studies with follow-up assessment in multiple domains, data from the various domains were extracted and assessed separately. Due to the potential confounding effect of preterm birth<sup>23</sup>, studies in which the growth impaired group mean gestational age (GA) fell below 35 weeks were analysed separately. This cut-off point for preterm birth was selected to include neonates delivered very preterm (<32 weeks) and 'moderately preterm' (<35 weeks)<sup>24</sup>. Birth at <35 weeks has been used as a cut-off point in a number of previous studies, and has been shown to have a specific risk factors<sup>25-27, 29-32</sup>, and an association with increased mortality<sup>25</sup> and morbidity<sup>26,27</sup>. Information from large population studies and impairment and disability registers (e.g. cerebral palsy registers) has also shown neonates born <35 weeks to have a higher rate of negative long-term health and social outcomes<sup>29,30</sup>, and poorer educational and behavioural outcomes (particularly in literacy, numeracy, motor skills and hyperactivity)<sup>31</sup>.

The quality of studies was evaluated using a quality assessment scale, which was based on existing checklists<sup>32,33</sup>, and modified to reflect the inclusion criteria of the present systematic review. The quality rating scale assessed the likelihood of bias in five methodological domains: the participant sample, the method by which fetal growth impairment was determined, the quality of

the follow-up assessment, the statistical analysis of the data, and the thoroughness of reporting the results.

### **2.2.3 Statistical analysis**

Data were organised into the domains of cognitive, language, motor, hearing, vision, behaviour and sleep. In the case of studies with follow-up assessment in multiple domains, data were extracted and classified separately. Studies were stratified according to GA at birth (<35<sup>+0</sup> and ≥35<sup>+0</sup> weeks of gestation), to identify any differential effects between these groups. In cases where a single cohort was followed up at multiple time-points, all assessments were retained as separate points in graphical representations.

Firstly, the standardised mean difference (SMD) between growth impaired and control groups was calculated for each domain in each study, according to Cohen's method<sup>34</sup>. The SMD was calculated by dividing the difference between the group means by the corresponding pooled SD. This score represents the group difference, expressed in units of SD, whereby a negative SMD indicates poorer neurodevelopmental outcomes in the growth impaired group relative to controls, a positive SMD indicates poorer neurodevelopmental outcomes in the controls relative to the growth impaired group, and an SMD of zero indicates no group difference. In cases where the results were presented as an Odds Ratio (OR), the OR was converted to the SMD using the method recommended by Chinn<sup>28</sup> (see equation below). For those studies where the SMD estimation was not possible (2 data points in total), the results were described independently.

$$SMD = \frac{\ln(OR)}{1.81}$$

The SMDs and trend lines were plotted graphically, with the size of each point reflecting the sample size of the study. Mean effect sizes were calculated for each domain as well as overall effects (pooled across domains). This statistical approach to quantifying effects was followed, as opposed to a formal meta-analytic approach, as potential differential effects across age at follow-up meant that formal meta-analytic methods may have been inappropriate. This analysis was also repeated by: 1) only including studies that had a definition of fetal growth impairment that included both size and abnormal Doppler; and 2) removing studies that were repeated follow-ups of the same cohort (retaining the study with the lowest risk of bias, indicated by highest quality rating score).

To identify the proportion of studies with effects co-occurring in simultaneous domains (for example, cognitive and behaviour), all papers that presented outcomes in multiple neurodevelopmental domains were assessed for the co-occurrence of simultaneous significant effects. The number of studies that identified concurrent effects in two domains within the same sample was calculated, and expressed as a proportion of the total number of studies that examined that particular pair of neurodevelopmental domains.

All analysis was conducted using IBM SPSS for Windows v21.0<sup>35</sup> and GraphPad Prism v6.0<sup>36</sup>.

## **2.3 Results**

The database search returned 28,861 reports, of which 1,368 were unpublished papers, dissertations and theses. A further 15 studies were identified from manual reference list searches. After removing duplicates and eliminating irrelevant titles and abstracts, 150 were selected for full text review (Figure 2.3).

Of these full text papers, 112 (75%) were excluded as they did not meet the inclusion criteria. The primary reasons for exclusion were failure to identify fetal growth impairment using ultrasound measures ( $n=66$ ), the use of non-standardised or unsuitable neurodevelopmental

outcome measures ( $n=18$ ), review papers ( $n=12$ ), follow-ups conducted in utero or only during the early neonatal period ( $n=5$ ), severe pregnancy complications ( $n=4$ ), insufficient sample size ( $n=4$ ) and conference proceedings ( $n=2$ ). Thirty-eight studies were included in the final analysis, of which 18 assessed the neurodevelopmental outcomes of growth impaired children born <35 weeks and 20 assessed the outcomes of growth impaired children born at  $\geq 35$  weeks of gestation. A total of 6,921 children were included, which were drawn from 7 longitudinally followed cohorts, and 16 experimental studies. All studies were conducted in populations from high-income countries (HICs) including Austria, Canada, Finland, Germany, Israel, Italy, the Netherlands, New Zealand, Spain, Sweden, Switzerland, UK and USA, and one was conducted in an upper-middle income country (Jamaica)<sup>6</sup>.

The quality of each study was scored out of a maximum 40 points, stratified into one of three categories: high risk of bias (0-19 points), medium risk of bias (20-30 points), and low risk of bias (31-40 points). Cut-off points for categorisation were determined based on mean and standard deviation (SD) of all quality rating scores ( $M=25.3$ ,  $SD=5.6$ ), such that those studies that fell more than one SD below or above the mean quality rating score were determined as high- or low-risk of bias, respectively (Figure 2.2). Ten studies did not adjust for the potential effects of confounding variables, and thus scored low on the confounder control quality criterion. Four studies accounted for GA at birth only, whereas 24 included additional maternal and child characteristics. Twenty studies accounted for family SES or some correlate (such as parental education/occupation).

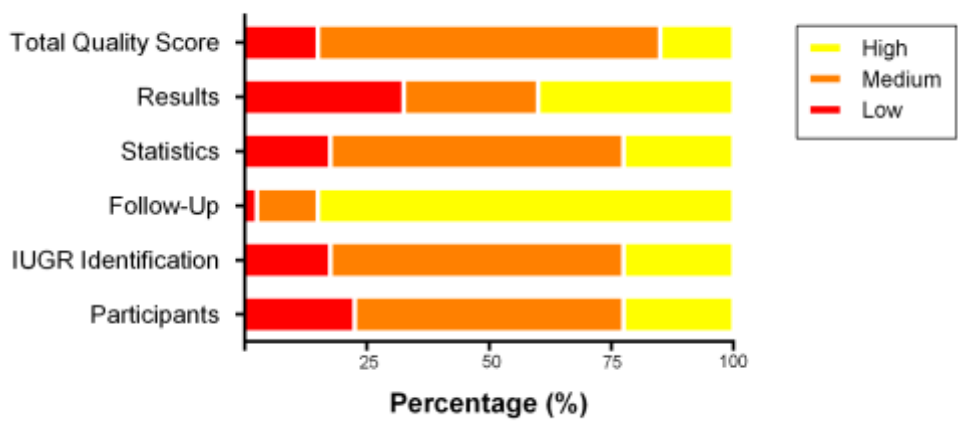


**Figure 2.2. Spread of quality rating scores across methodological domain**

A comprehensive description of all studies included is presented in the Supplementary Tables (Appendix I). All reporting was conducted according to the PRISMA reporting standards for systematic reviews and meta-analyses<sup>37</sup> (Appendix II). The definitions used for the growth impaired and corresponding control groups, the domains evaluated and the descriptive statistics are presented in Table 2.1 and Table 2.2.

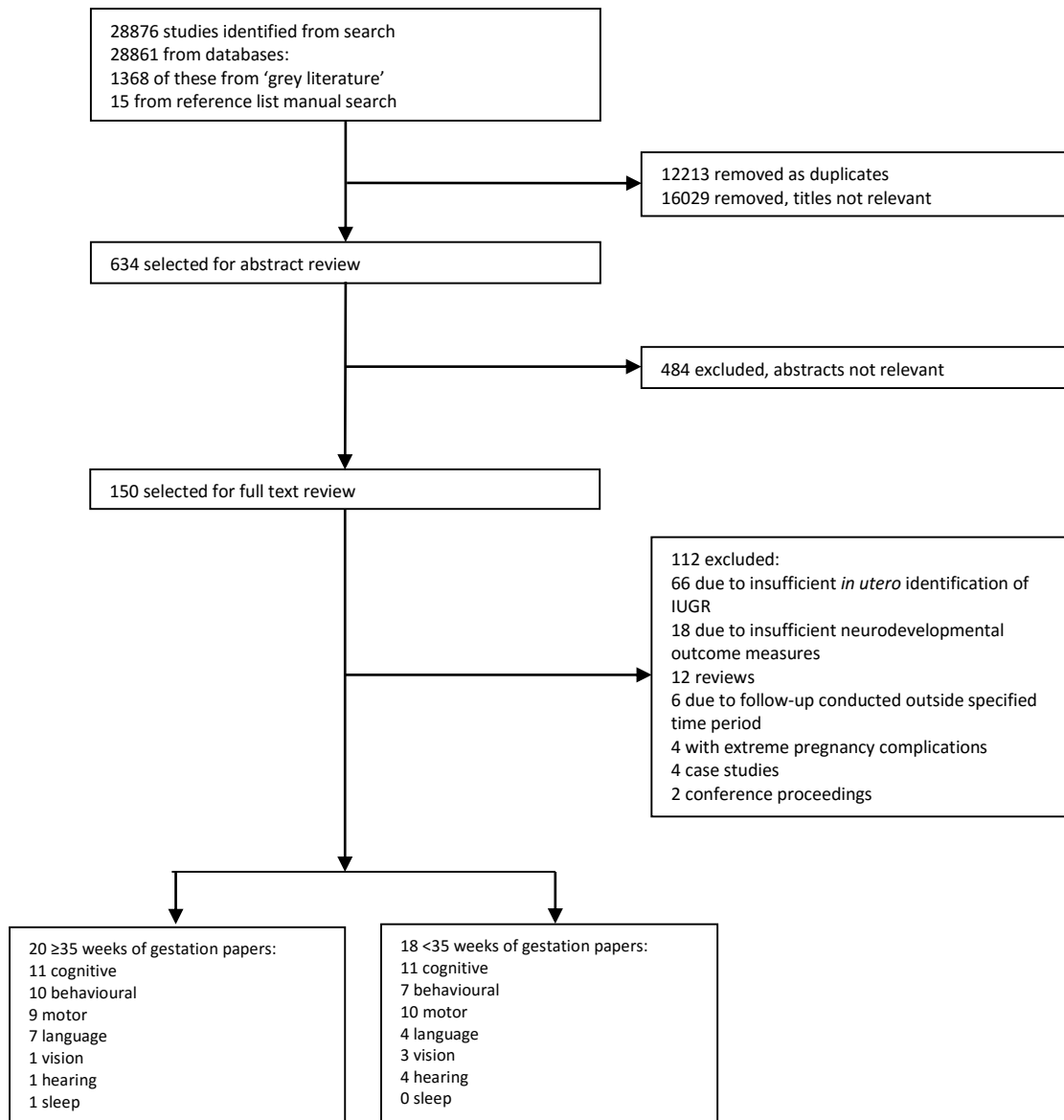


Figure 2.3. Literature review and search results

### **2.3.1 Fetal growth impairment and neurodevelopmental outcomes in children born at $\geq 35$ weeks of gestation**

In all studies, fetal growth impairment was identified by serial measures of HC or BPD in which at least one was below the 10<sup>th</sup> percentile according to local standards during mid-late pregnancy, and confirmed by birth anthropometric measures (Table 2.1). In studies in which the diagnosis of growth impairment was made by abnormal Doppler velocimetry, abnormal Doppler indices were primarily identified in umbilical and middle cerebral arteries in the final assessment prior to birth, confirmed by anthropometric measures at birth. The median BW for growth impaired neonates was 1862g (range = 1800 – 2883g) and the median GA at birth was 37<sup>+4</sup> weeks (range = 36<sup>+0</sup> – 40<sup>+3</sup> weeks of gestation).

In 18 studies the control group was defined as having an appropriate-for-gestational-age (AGA) BW using local or regional growth charts. Two studies used control groups consisting of both SGA and AGA infants but with normal Doppler indices. Although the majority of controls were term infants ( $\geq 37^{+0}$  weeks of gestation), 4 studies included a small proportion of preterm AGA neonates.

**Table 2.1. Descriptive characteristics of growth impaired and control groups born at ≥35 weeks of gestation**

| Study                                      | Sample Size<br>Case/Control             | M BW (growth<br>impaired)              | M GA at Birth (growth<br>impaired)     | Domains                   | Fetal growth impairment definition                                                                      |                     | Control Characteristics                           |
|--------------------------------------------|-----------------------------------------|----------------------------------------|----------------------------------------|---------------------------|---------------------------------------------------------------------------------------------------------|---------------------|---------------------------------------------------|
|                                            |                                         |                                        |                                        |                           | In utero identification                                                                                 | Growth<br>phenotype |                                                   |
| Ley et al., 1996 <sup>38</sup>             | 41/105                                  | 2883(521)                              | 39-0(1-8)                              | M (6.5 yrs)               | AREDFV in DAo                                                                                           | Weight              | Mixed AGA/SGA, mixed term/preterm, normal Doppler |
| Ley et al., 1996b <sup>39</sup>            | 21/105                                  | >2 SD below mean                       | >37 weeks                              | C, L (7 yrs)              | REDFV in DAo                                                                                            | Weight              | Mixed AGA/SGA, mixed term/preterm, normal Doppler |
| Eixarch et al., 2008 <sup>40</sup>         | Non-redis=25<br>Redis=100<br>Control=97 | Non-Redis=2521(246)<br>Redis=2567(302) | Non-Redis=39-6(1-4)<br>Redis=39-7(1-4) | C, B, L, M (2 yrs)        | UA-PI >95 <sup>th</sup> percentile. FCR = IUGR as above and MCA-PI<5 <sup>th</sup> percentile           | Weight              | AGA, term, normal Doppler                         |
| Leijon et al., 1980 <sup>41</sup>          | 29/47                                   | 2020(320)                              | 37-6(1-8)                              | B, H, L, M (5,10,18 mths) | Severe GI = BPD≤2SD from mean<br>GI = BPD 1-2SD from mean                                               | Weight              | AGA, term, normal Doppler                         |
| McCowan et al., 2002* <sup>42</sup>        | 220                                     | 2095(549)                              | 36-5(2-7)                              | C, B (18 mths)            | AREDFV in UA                                                                                            | Weight              | SGA, mixed term and preterm (cohort study)        |
| Geva et al., 2006 <sup>43</sup>            | 123/63                                  | 1853(416)                              | 37-0(2-6)                              | C, B, M(9 yrs)            | Late mid-second-third trimester, HC growth restriction                                                  | Stunted             | AGA, mixed (33.8% preterm)                        |
| Geva et al., 2006b <sup>44</sup>           | 110/61                                  | 1853(416)                              | 37-0(2-6)                              | C (9 yrs)                 | Late mid-second-third trimester, HC growth restriction                                                  | Stunted             | AGA, term                                         |
| Walker et al., 2007* <sup>6</sup>          | 186                                     | 3190(460)                              | 39-7(1-3)                              | C, L (6-8 yrs)            | Measurements of HC, BPD, FL, AC acquired in early-, mid- and late-gestation                             | Stunted             | AGA, term (cohort study)                          |
| Fattal-Valevski et al., 1999 <sup>45</sup> | 85/42                                   | 1860(407)                              | 37-5(2-1)                              | C, M (3 yrs)              | Late mid-second-third trimester, HC growth restriction. FCR= CI >1SD of control M                       | Stunted             | AGA, mixed (15% preterm)                          |
| Harvey et al., 1982 <sup>5</sup>           | Pre-26=10<br>Post-26=41<br>Control=41   | 1800(440)                              | >37 weeks                              | C, L, M (3-7 yrs)         | Weekly growth increment in BPD <5 <sup>th</sup> percentile over ≥2 weeks, compared to normal BPD curves | Stunted             | AGA, term                                         |
| Gazzolo et al., 1995 <sup>46</sup>         | 22/96                                   | 2023(466)                              | 36-0(3-0)                              | M (8 mths)                | BPD and AC <10 <sup>th</sup> percentile and RI of UA >90 <sup>th</sup> percentile                       | Stunted             | AGA                                               |



| Study                                 | Sample Size<br>Case/Control | M BW (growth<br>impaired) | M GA at Birth (growth<br>impaired)  | Domains            | Fetal growth impairment definition                                               |         | Control Characteristics   |
|---------------------------------------|-----------------------------|---------------------------|-------------------------------------|--------------------|----------------------------------------------------------------------------------|---------|---------------------------|
| Henrichs et al., 2009 <sup>*4</sup>   | 4384                        | 3464(536)                 | 40-0(1-6)                           | B, M (12 mths)     | Fetal growth = SD of size in late pregnancy – SD of size in mid pregnancy        | Stunted | AGA, term (cohort study)  |
| Thordstein et al., 2004 <sup>47</sup> | 33/21                       | 1809(551)                 | 36-0(3-0)                           | V (6 wks)          | Increase in EFW <10% of M between 2 measurements separated by 12 days            | Stunted | AGA, term, normal Doppler |
| Henrichs et al., 2008 <sup>*48</sup>  | 3985                        | 3480(480)                 | 40-0(1-14)                          | B (3 mths)         | Fetal growth = size in late pregnancy – size in mid pregnancy                    | Wasted  | AGA, term (cohort study)  |
| Roza et al., 2008b <sup>* 49</sup>    | 3792                        | 3532(545)                 | Median =40-3<br>Range=36-0-42-4)    | B (6 mths)         | Latent growth curve modelling used to obtain fetal growth scores.                | Wasted  | AGA, term (cohort study)  |
| Roza et al., 2008 <sup>* 50</sup>     | 1135                        | 3589(532)                 | Median = 40-4<br>Range = 37-0-42-6) | B (18 mths)        | FCR based on U/C ratio. U/C ratio = UA-PI/CA-PI                                  | Wasted  | AGA, term (cohort study)  |
| Leitner et al., 2002 <sup>51</sup>    | 26/47                       | Not stated                | Not stated                          | S, B (4-7 yrs)     | Late mid-second-third trimester HC growth restriction                            | Wasted  | AGA                       |
| Leitner et al., 2000 <sup>52</sup>    | 81/41                       | 1864(401)                 | 37-6(2-2)                           | C, M (6-7 yrs)     | Late mid-second-third trimester HC growth restriction. FCR= CI >1SD of control M | Wasted  | AGA, term, normal Doppler |
| Lietner et al., 2005 <sup>53</sup>    | 28/29                       | 1826(49)                  | 36-5(2-9)                           | C (9-10 yrs)       | Late mid-second-third trimester, HC growth restriction                           | Wasted  | AGA, term, normal Doppler |
| Leitner et al., 2007 <sup>54</sup>    | 123/63                      | 1842(411)                 | 36-9(2-6)                           | C, B, M (9-10 yrs) | Late mid-second-third trimester, growth restriction. FCR = CI >1SD of control M  | Wasted  | AGA, term                 |

AGA=appropriate for gestational age; SU=serial ultrasound; DV=Doppler velocimetry; wks = weeks; mths = months; yrs = years; GI = growth impairment; BPD = biparietal diameter; MCA = middle cerebral artery; UA = umbilical artery; DV = ductus venosus; U/C = umbilical/cerebral; FGR =fetal growth impairment; PI = pulsatility index; EFW = estimated fetal weight; BW = birth weight; \*= regression study, control variables shown are whole cohort averages. 1= Growth impairment confirmed by birth weight <10th percentile, according to local standards; 2= Growth impairment confirmed by birth weight 1-2 SDs below mean, according to local standards; 3= Growth impairment confirmed by BPD/AC 1-2 SDs below mean, according to local standards; DAo= descending aorta; C = cognitive; L = language; B = behaviour; M = motor; H = hearing; V = vision; S = sleep.

All 20 studies that examined neurodevelopmental outcomes in children with growth impairment, born at  $\geq 35$  weeks of gestation, identified an association between growth impairment and poor neurodevelopmental outcomes in at least one domain, in comparison to the corresponding control groups (Figure 2.4). The extent of neurodevelopmental deficit varied by domain (Table S2.2), with a mean neurodevelopmental deficit across all domains of 0.51 SMD among growth impaired children compared to controls. Growth impaired children were particularly negatively affected in the domains of cognitive (0.52 SMD) and behaviour (0.47 SMD) development, with a number of studies identifying attention impairments. Vision and sleep development were also impaired, however these estimates are based on single studies and must be interpreted with caution. Two of the studies for which SMD could not be estimated were regression analyses which presented only beta-coefficients<sup>48,49</sup>. Both these studies showed growth impairment to be associated with poor behaviour outcomes at 3 and 6 months, respectively ( $\beta = -15.6$ , 95%CI = -23.8 to -7.31;  $\beta = -0.53$ , 95%CI = -0.82 to -0.24), although the significance of the association was not upheld in the study examining behaviour at 6 months after adjustment for confounding variables. In the cognitive domain, there appeared to be a trend of increasing SMDs over advancing postnatal age, however no such trend was identifiable in the behavioural, motor or language domains. Trend lines were not depicted for the hearing, vision or sleep domains due to insufficient data points.

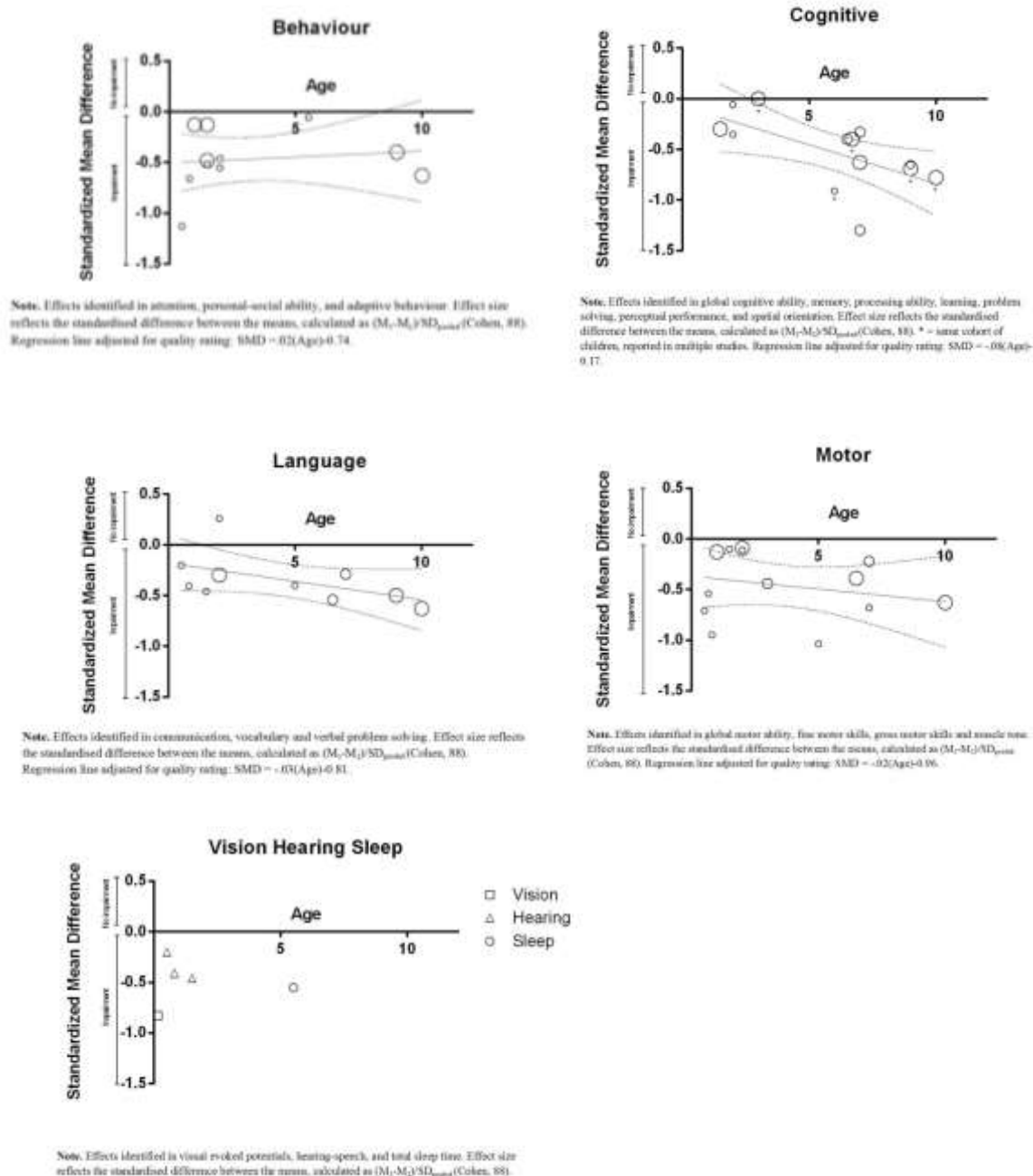


Figure 2.4. The association between standardised mean differences (SMDs) across postnatal age in different neurodevelopmental domains in children born  $\geq 35$  weeks of gestation

Data on studies that defined growth impairment by both abnormal Doppler *and* small size at birth were available for a total of 4 studies in the cognitive, behavioural, language and motor domains (Table S2.3). Using this definition, growth restriction was associated with an overall neurodevelopmental impairment of 0.34 SMD (compared to 0.45 SMD across these domains using the original definition). This result however must be interpreted with caution due to the small sample size. Re-analysis, removing studies with multiple follow-ups, showed growth impairment to be associated with an overall neurodevelopmental deficit of 0.52 SMD, an increase of 0.01 SMD compared to the original analysis (Table S2.4).

### **2.3.1.1 Behavioural development**

Ten papers examining behavioural outcomes in growth impaired children born  $\geq 35$  weeks of gestation were identified. Of these 10 studies, 9 identified a significant effect of growth impairment on behavioural outcomes, with the earliest study reporting an effect on behavioural development at 3 months of age (Table S2.5). Significant differences were most commonly identified in the domains of attention/hyperactivity. SMDs ranged from 0.06-1.13, however for two studies SMD could not be estimated. These presented beta-coefficients from regression analyses<sup>29,30</sup>, and showed fetal growth impairment to be associated with poorer behaviour outcomes at 3 and 6 months ( $\beta = -15.6$ , 95%CI = -23.8 to -7.31;  $\beta = -0.53$ , 95%CI = -0.82 to -0.24 respectively).

### **2.3.1.2 Cognitive development**

Eleven papers examining cognitive outcomes in children with fetal growth impairment born  $\geq 35$  weeks of gestation were identified (Table S2.6). Six of these studies were conducted on the same cohort, born at the Lis Maternity Hospital, Tel Aviv Sourasky Medical Centre, with follow-ups occurring at different times throughout childhood. Of the 11 studies included in the cognitive development analysis, 10 identified fetal growth impairment to lead to significant deficits. It is important to note that whilst growth impaired children score significantly lower on

many cognitive domains, they remain in the “normal range” for developmental age, with studies reporting global cognitive scores ranging from 95.6<sup>42</sup>-102.9<sup>5</sup>. Global cognitive deficits were the most commonly affected cognitive domain (5 studies), and SMDs ranged from 0.00-1.59.

#### **2.3.1.3 Language development**

Seven papers examined language outcomes in children with fetal growth impairment born  $\geq 35$  weeks of gestation (Table S2.7). Of these studies, 3 demonstrated growth impairment to be associated with deficits in language development, including the two highest quality studies in this domain<sup>40,43</sup>. Growth impairment was identified to lead to significant deficits in overall verbal IQ<sup>38</sup>, as well as the specific domains of communication<sup>40</sup>, vocabulary<sup>43</sup>, and verbal problem solving<sup>43</sup>. The single study which used regression analysis<sup>6</sup>, however, did not identify fetal growth at 14, 25 or 35 weeks GA to be associated with language outcomes, despite being associated with general cognitive outcomes. SMDs ranged from -0.26-0.54.

#### **2.3.1.4 Motor development**

Nine papers examining motor outcomes of children with fetal growth impairment born  $\geq 35$  weeks of gestation were identified (Table S2.8). Of these 9 papers, 8 identified fetal growth impairment to lead to significant motor deficits (seven of which identified deficits in multiple motor domains). Six papers identified growth impairment to lead to deficits in fine motor skills, and 6 identified deficits in gross motor skills. Interestingly, the effect of fetal growth impairment on overall motor ability was demonstrated to be stronger when growth restriction was early-onset (pre-26 weeks GA), as opposed to late onset (SMD=0.64). SMDs ranged from 0.09-1.23.

The regression analysis study<sup>4</sup> identified fine motor development to be significantly associated with the rate of fetal HC growth in early-to-mid pregnancy ( $OR=0.85$ , 95%  $CI=0.73-0.98$ ) and mid-to-late pregnancy ( $OR=0.81$ , 95%  $CI=0.70-0.93$ ). Gross motor development was identified to be significantly associated with a higher velocity increase in fetal weight from mid-to-late pregnancy ( $OR=0.90$ , 95%  $CI=0.82-0.99$ ). These associations persisted after adjusting for

sex, maternal age, maternal pre-pregnancy BMI, maternal education, maternal smoking and alcohol use during pregnancy, child ethnicity, maternal depression at child age 2 months, child age at follow-up, and the corresponding fetal size characteristic in early or mid-pregnancy.

#### **2.3.1.5 Vision**

One study examined the effects of fetal growth impairment on the visual system during childhood in children born  $\geq 35$  weeks of gestation (Table S2.9). This study, conducted on a Swedish sample of 51 infants (33 growth impaired), examined visual evoked potentials at 40 and 46 weeks GA, however as follow-up assessments conducted within the neonatal period are excluded from the current systematic review, only the 46 week GA assessment was retained for analysis. Infants with fetal growth impairment were determined to have significantly prolonged P latencies at both 0.1 and 0.3Hz of stimulation, with large SMDs identified, of 0.83 and 0.77 respectively.

#### **2.3.1.6 Hearing**

One study examined the effect of fetal growth impairment on hearing development in children born at  $\geq 35$  weeks of gestation (Table S2.10). This study, conducted on a Swedish sample of 47 infants (29 growth impaired), did not identify any significant difference between growth impaired and control children at 5, 10 or 18 months in the hearing-speech domain of Griffiths' Mental Development Scales ( $p > .05$ ).

#### **2.3.1.7 Sleep**

Only a single study examined the effects of fetal growth impairment on sleep in children born  $\geq 35$  weeks of gestation, followed-up at ages four to seven years (Table S2.11). This study, conducted on an Israeli sample of 73 children (26 growth impaired), examined a range of sleep variables using actigraphy, including sleep onset time, sleep period, true sleep time, sleep efficiency, number of waking episodes and motionless sleep percentage. The only variable

identified to be significantly associated with growth impairment was true sleep time, which was lower than in control children. The effect size was moderate (SMD=0.55).

### **2.3.2 Fetal growth impairment and neurodevelopment outcomes in children born at <35 weeks of gestation**

In 17 of the 18 studies in this group, the diagnosis of fetal growth impairment was made by abnormal Doppler velocimetry in the umbilical and middle cerebral arteries in the final antenatal assessment, and confirmed by anthropometric measures at birth. One study diagnosed fetal growth impairment by serial measures of HC below the 10<sup>th</sup> percentile during mid-late pregnancy, confirmed at birth. The median BW for growth impaired neonates was 1054g (range = 642 – 1473g) and the median GA at birth was 30<sup>+2</sup> weeks of gestation (range = 27<sup>+0</sup> – 34<sup>+3</sup> weeks) (Table 2.2).

In 15 studies, the controls consisted of preterm infants matched for GA. Three studies included term infants, 2 of which used normal Doppler indices as indicators of normal fetal development. Twelve studies included only AGA infants as controls, and the remaining studies selected a heterogeneous control group, consisting of both AGA and SGA infants, but all with normal Doppler indices.

**Table 2.2. Descriptive characteristics of growth impaired and control groups born at <35 weeks of gestation**

| Study                                  | Sample Size<br>Case/Control       | M BW (growth<br>impaired)                            | M GA at Birth (growth<br>impaired)          | Domains                 | Growth impairment definition                                                                                   |                     | Control Characteristics                          |
|----------------------------------------|-----------------------------------|------------------------------------------------------|---------------------------------------------|-------------------------|----------------------------------------------------------------------------------------------------------------|---------------------|--------------------------------------------------|
|                                        |                                   |                                                      |                                             |                         | In utero identification                                                                                        | Growth<br>phenotype |                                                  |
| Vossbeck et al., 2001 <sup>55</sup>    | 16/16                             | Median = 545<br>Range = 376-1020                     | Median = 27.0<br>Range = 25.0-29.0          | C, M (3-91<br>mths)     | AREDFV in UA                                                                                                   | Weight              | AGA, preterm, normal<br>Doppler                  |
| Scherjon et al., 1996 <sup>56</sup>    | 34/56                             | Median=1190(314)                                     | 31.5(1.7)                                   | V (6 mths)              | FGR <0.75. FCR = U/C ratio >0.725                                                                              | Weight              | AGA, preterm, normal<br>Doppler                  |
| Padilla et al., 2010 <sup>57</sup>     | 37/36                             | 981.2(375.1)                                         | 30.0(3.0)                                   | C, M (18<br>mths)       | UA-PI>2SD and ultrasound EFW <10 <sup>th</sup><br>percentile                                                   | Weight              | AGA, preterm                                     |
| Padilla et al., 2011 <sup>58</sup>     | 20/20                             | 1060(310)                                            | 32.1(2.05)                                  | C, B, L, M<br>(18 mths) | Fetal weight <10 <sup>th</sup> percentile and UA- PI >2<br>SD                                                  | Weight              | AGA, term, normal<br>Doppler                     |
| Torrance et al., 2010 <sup>59</sup>    | 71                                | 875(217)                                             | 30.2(1.9)                                   | C (18-24<br>mths)       | UA-PI > 2SD from M                                                                                             | Weight              | SGA, preterm, abnormal<br>Doppler (cohort study) |
| Valcamonico et al., 2007 <sup>60</sup> | 84                                | M=766 (-)                                            | M=29.0 (-)                                  | B, L, V (2 yrs)         | UA-PI > 2SD from M                                                                                             | Weight              | AGA, preterm, normal<br>Doppler                  |
| Fouron et al., 2001 <sup>61</sup>      | 30/14                             | 1421(619)                                            | 33.6(1.3)                                   | C, M (2-4<br>yrs)       | Retrograde Aol flow and UA-PI>95 <sup>th</sup><br>percentile                                                   | Weight              | Anterograde isthmic flow<br>i.e.normal           |
| Scherjon et al., 1998 <sup>62</sup>    | 34/62                             | Median = 1295<br>Range = 605-2295                    | Median = 30.4<br>Range = 26.2-32.8          | B, L, M (3<br>yrs)      | FCR=U/C ratio > 0.72                                                                                           | Weight              | AGA, preterm, normal<br>Doppler (cohort study)   |
| Kutschera et al., 2002 <sup>12</sup>   | AREDFV=16<br>ABF=15<br>Control=31 | AREDFV = 990 (610-<br>1630)<br>ABF = 1190 (535-2210) | AREDFV = 31.0 (28-36)<br>ABF = 33.0 (27-39) | C (3-6 yrs)             | AREDFV in UA (AREDFV group). FCR =<br>increased UA-PI, decreased MCA-PI or<br>increased U/C ratio (ABF group). | Weight              | AGA, preterm, normal<br>Doppler                  |
| Scherjon et al., 2000 <sup>63</sup>    | 28/45                             | 1400 (331)                                           | 29.6 (1.6)                                  | C (5 yrs)               | FCR = U/C ratio >0.725                                                                                         | Weight              | AGA, preterm, normal<br>Doppler (cohort study)   |
| Morsing et al., 2011 <sup>64</sup>     | 34/34                             | Median = 642<br>Range = 395-976                      | 27.0(1.4)                                   | C, B (5-8 yrs)          | AREDFV in UA                                                                                                   | Weight              | 2 control groups<br>1.AGA/Term<br>2.AGA/Preterm  |



| Study                                    | Sample Size<br>Case/Control | M BW (growth<br>impaired)                | M GA at Birth (growth<br>impaired)       | Domains                        | Growth impairment definition                                                        | Control Characteristics                           |
|------------------------------------------|-----------------------------|------------------------------------------|------------------------------------------|--------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------|
| Schreuder et al., 2002 <sup>65</sup>     | 36/40                       | 950(206)                                 | 30.0(2.0)                                | C, B, H, V, L, M<br>(5-12 yrs) | REDFV in UA                                                                         | Weight<br>SGA, preterm, normal Doppler            |
| Leppanen et al., 2010 <sup>66</sup>      | 16/54                       | 968(284)                                 | 29.0(0.6)                                | C, M (2 yrs)                   | UA-PI >95 <sup>th</sup> percentile. FCR = UA-PI/MCA-PI >95 <sup>th</sup> percentile | Stunted<br>Mixed AGA/SGA, preterm, normal Doppler |
| Kok et al., 2007 <sup>67</sup>           | 31/58                       | Redist=1137(307)<br>Non-Redist=1378(318) | Redist=30.5(1.8)<br>Non-Redist=29.4(1.9) | V, M (11 yrs)                  | FCR = U/C ratio >0.72                                                               | Stunted<br>Preterm, no brain sparing              |
| Bassan et al., 2011 <sup>68</sup>        | 114/193                     | 1473(310)                                | 34.5(1.6)                                | C (2 yrs)                      | Late mid-second-third trimester HC growth restriction. FCR= CI >1SD of control M    | Wasted<br>Term                                    |
| Baschat et al., 2009 <sup>69</sup>       | 72                          | Median=933<br>Range=490-2160             | Median=30.4<br>Range=25.5-37.2           | M, H, L<br>(2 yrs)             | AC < 5 <sup>th</sup> percentile, elevated UA-PI, and elevated DV-PI>2 SD            | Wasted<br>Preterm, normal Doppler (cohort study)  |
| Wienerroither et al., 2001 <sup>70</sup> | 23/23                       | 1258(482.9)                              | 34.1(3.5)                                | C, B, M, H<br>(5-8 yrs)        | AC <10 <sup>th</sup> percentile and AREDFV in UA                                    | Wasted<br>AGA, preterm, normal Doppler            |
| van den Broek et al., 2010 <sup>71</sup> | 89                          | 1137(307)                                | 30.5(1.7)                                | B (11 yrs)                     | FGR<0.80. FCR = U/C ratio > 0.72.                                                   | Wasted<br>AGA, preterm, normal Doppler            |

AGA=appropriate for gestational age; SU=serial ultrasound; DV=Doppler velocimetry; wks = weeks; mths = months; yrs = years; BPD = biparietal diameter; MCA = middle cerebral artery; UA = umbilical artery; DV = ductus venosus; U/C = umbilical/cerebral; FGR =fetal growth impairment; PI = pulsatility index; EFW = estimated fetal weight; BW = birth weight; \* = regression study, control variables shown are whole cohort averages. 1= Growth impairment confirmed by birth weight <10th percentile, according to local standards; 2= Growth impairment confirmed by birth weight 1-2 SDs below mean, according to local standards; 3= Growth impairment confirmed by BPD/AC 1-2 SDs below mean, according to local standards; DAo= descending aorta; C = cognitive; L = language; B = behaviour; M = motor; H = hearing; V = vision; S = sleep.

Of the 18 studies, 16 identified an association between fetal growth impairment and difficulties in at least one neurodevelopmental domain. SMD was estimated for all comparisons in this group but one<sup>70</sup> (Figure 2.5). In comparison to the growth impaired children born  $\geq 35$  weeks of gestation, those born  $< 35$  weeks of gestation experienced a higher level of neurodevelopmental impairment across all domains, with an average additional impairment of 0.2 SMD. The exception to this was in the domains of hearing and motor development, in which the mean impairment in growth impaired children born  $\geq 35$  weeks and  $< 35$  weeks of gestation were similar. Vision and sleep outcomes did not have sufficient data to compare SMD for children in these two gestational age groups.

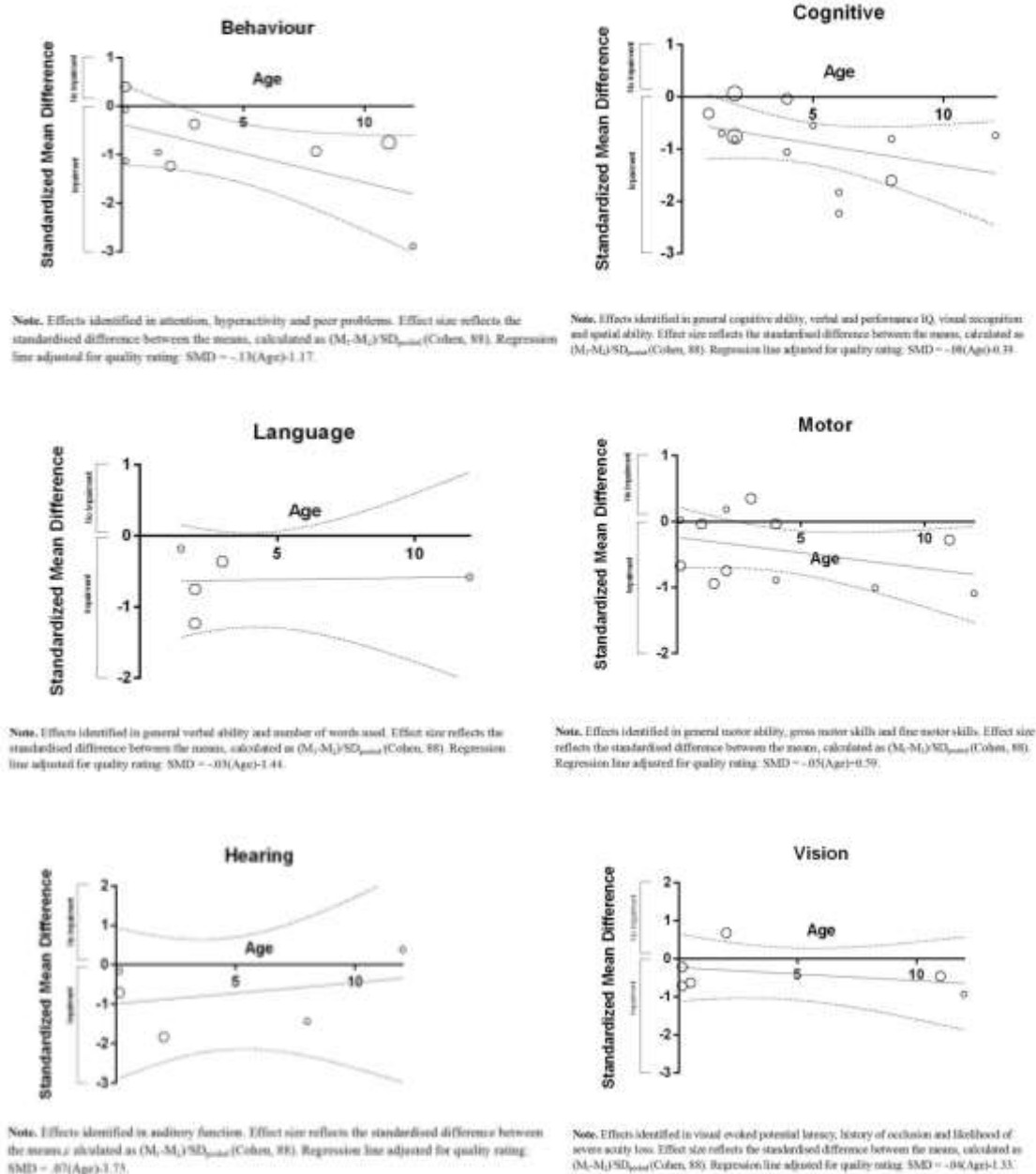


Figure 2.5. The association between standardised mean differences (SMDs) across postnatal age in different neurodevelopmental domains in children born <35 weeks of gestation.

Data on studies that defined fetal growth impairment by both abnormal Doppler and birth anthropometry were available for a total of ten studies (*M* and *SD* by domain presented in Table S2.3). Using this definition, fetal growth impairment was associated with an overall neurodevelopmental deficit of 0.90 SMD, compared to 0.71 SMD using the original definition. Re-analysis removing studies with multiple follow-ups showed growth impairment to be associated with an overall neurodevelopmental deficit of 0.74 SMD, an increase of 0.03 SMD compared to the original analysis (Table S2.4).

### **2.3.2.1 Behavioural development**

Seven papers examining behavioural outcomes of growth impaired children born <35 weeks of gestation were identified (Table S2.12). Of these seven studies, five showed a significant effect of fetal growth impairment on behavioural outcomes. SMDs ranged from 0.07-2.90. Significant effects were identified in the domains of attention<sup>64,70</sup> and hyperactivity<sup>65</sup>. One study examined the association between fetal growth and behavioural outcomes using regression analysis<sup>71</sup>, and identified a significant association between impaired fetal growth and internalizing behaviour problems (*OR*=3.90, *95%CI*=1.4-10.9, *p*=.008).

### **2.3.2.2 Cognitive development**

Eleven papers examined cognitive outcomes of growth impaired children born <35 weeks, predominantly using Doppler velocimetry (Table S2.13), confirmed by birth anthropometry. Of these, 7 identified a significant effect of growth impairment on cognitive outcomes. Significant effects were mostly identified in general cognitive ability (5 studies). One study conducted a regression analysis to identify the significant predictors of a low score on the Bayley or Griffiths assessments (<85)<sup>59</sup>. Significant predictors of impaired cognitive ability in growth impaired children were identified as BW <2.3<sup>rd</sup> percentile (*OR*=3.95, *95%CI*=1.55-10.10, *p*<.01), an umbilical artery pH <7.0 (*OR*=8.98, *95%CI*=1.82-44.21, *p*<.001), the presence of

placental villitis ( $OR=3.19$ ,  $95\%CI=1.26-8.09$ ,  $p<.05$ ) and primiparity ( $OR=0.38$ ,  $95\%CI=0.16-0.92$ ,  $p<.05$ ), accounting for 24% of the variation in cognitive outcome. SMDs ranged from 0.04-2.35.

### **2.3.2.3 Language development**

Four papers examining the language outcomes of growth impaired children born <35 weeks of gestation were identified (Table S2.14). Of these four studies, only one identified an effect of fetal growth impairment on language outcomes, and this was within a broader classification of 'neurological deficit', so must be interpreted with caution. Fetal growth impairment was not demonstrated to have an effect on general verbal ability<sup>65</sup>, use of the pronoun 'I'<sup>62</sup>, comprehensibility<sup>62</sup>, parental rating of adequate speech<sup>62</sup>, or number of words used<sup>62</sup>. The single regression study did not identify a significant association between abnormal Doppler measurements (ductus venosus and umbilical artery) and expressive language ( $p>.05$ ). SMDs ranged from 0.14-1.23.

### **2.3.2.4 Motor development**

Ten studies examined the effects of fetal growth impairment on motor development in children born <35 weeks of gestation (Table S2.15). The results of the between groups studies suggest that fetal growth impairment may not confer an additional risk factor for motor impairment following very preterm births, with only five (50%) identifying a significant effect. These motor studies examined a range of motor outcomes including overall motor abilities (6 studies), gross motor (4 studies) and fine motor (4 studies). The studies identified fetal growth impairment to have a significant effect on motor development reported effects in overall motor ability and fine motor ability. The regression analysis study<sup>69</sup> identified a significant association between an abnormal ductus venosus Doppler index and overall motor ability ( $OR=3.90$ ,  $95\%CI=1.4-11.0$ ,  $p=.009$ ), with an increased likelihood ratio of 3.90 ( $95\%CI=1.4-11.0$ ). SMDs ranged from 0.02-1.09.

### **2.3.2.5 Vision**

Three papers examined the effect of fetal growth impairment on visual development in children born at <35 weeks of gestation, with all identifying negative visual function outcomes (Table S2.16). Growth impaired infants who were delivered very preterm were identified to have significantly poorer general visual responses<sup>72</sup> (SMD=0.72,  $p=.004$ ), and have a higher likelihood of severe acuity loss<sup>65</sup> ( $p=.014$ ). The effect sizes were moderate-to-high (SMDs=0.46-0.93).

### **2.3.2.6 Hearing**

Four papers examined the hearing outcomes in growth impaired children born <35 weeks gestation (Table S2.17). Of these 4 papers, 3 identified growth impairment to significantly disturb hearing function in childhood. Hearing difficulties were identified in general auditory function. The regression analysis study in growth impaired infants born at <35 weeks of gestation identified REDFV in the UA to be significantly associated with abnormal hearing outcomes, with a large OR ( $OR=27.40$ ,  $95\%CI=3.1-243.1$ ,  $p<.0001$ ). SMDs ranged from 0.16-1.83.

## **2.3.3 The specific effects of stunting and wasting on child neurodevelopment**

Growth impairment was confirmed by indices of BW in 5 papers in the  $\geq 35$  weeks of gestation group and 12 papers in the <35 weeks of gestation group. Papers using BW as an indicator of fetal growth impairment most commonly used weight-for-gestational age, followed by crude weight (e.g. <2500g). The growth impairment phenotype was identified as stunted in 8 papers in the  $\geq 35$  weeks of gestation group and 2 papers in the <35 weeks of gestation group. Stunted growth was most commonly identified by small HC, followed by biparietal diameter and femur length. The growth impairment phenotype was identified as wasted in 7 papers in the  $\geq 35$  weeks of gestation group and 4 papers in the <35 weeks of gestation group. Wasting was most commonly identified by asymmetric growth, typically a small AC compared to HC or small AC compared to crown-heel length.

In the  $\geq 35$  weeks of gestation group, growth impairment defined by BW was shown to have an overall neurodevelopmental impairment of -0.38 SMD (range = 0.26 to -1.13). Stunting was associated with a mean overall neurodevelopmental deficit of -0.56 SMD (range = -0.22 to -1.30), and wasting was associated with a mean overall neurodevelopmental deficit of -0.51 SMD (range = -0.06 to -0.91). Stunting was shown to have the strongest effects on visual and cognitive development, and wasting on cognitive and language development.

In the  $< 35$  weeks of gestation group, growth impairment identified by BW was shown to have an overall neurodevelopmental impairment of -0.58 SMD (range = -0.04 to -2.89). Stunting was associated with a mean overall neurodevelopmental deficit of -0.37 SMD (range = -0.28 to -0.46), and wasting was associated with a mean overall neurodevelopmental deficit of -0.94 SMD (range = -0.37 to -1.63). Stunting was shown to have the strongest effect on visual development, and wasting on hearing development, although caution must be taken when interpreting results as only a small number of studies examined these growth phenotypes in the  $< 35$  week GA group.

#### **2.3.4 Fetal circulatory redistribution (FCR) and child neurodevelopment**

The association between FCR and neurodevelopment was examined in 8 papers in the  $\geq 35$  weeks of gestation group, and 10 papers in the  $< 35$  weeks of gestation group. These papers compared growth impaired cases with in utero signs of FCR to controls (defined as AGA without FCR). A further 2 papers in neonates born  $\geq 35$  weeks of gestation, and 2 papers in those born  $< 35$  weeks of gestation compared the outcomes of children with fetal growth impairment with FCR to those with growth impairment without FCR. This comparison allows examination of the role of FCR as either a 'protective' mechanism or a marker of the severity of disturbance to the fetal growth process.

In the  $\geq 35$  weeks of gestation group, all studies that compared growth impaired FCR cases to AGA non-FCR controls showed growth impaired FCR cases to have greater

neurodevelopmental deficit during childhood (SMD range = -0.18 to -0.91). The studies that compared growth impaired *with* FCR to growth impaired *without* FCR, identified the presence of FCR to lead to greater neurodevelopmental deficit (SMD range = -0.46 to -0.63), indicating that FCR confers an approximate 0.5 SD additional deficit on overall neurodevelopment in the presence of fetal growth impairment. FCR in babies born  $\geq 35$  weeks gestation was associated with deficit in behaviour, cognition, and language, and also with prolonged VEP latencies.

In the  $< 35$  weeks of gestation group, 7 of the 10 studies that compared growth impaired-FCR cases to AGA non-FCR controls, identified FCR cases to have increased neurodevelopmental deficits during childhood (SMD range = -0.37 to -1.83). The remaining 3 studies did not identify any difference between growth impaired-FCR babies and AGA non-FCR controls (SMD range = 0.07 to -0.04). The studies that compared growth impaired cases with and without FCR identified FCR to lead to greater neurodevelopmental deficit. Children with fetal growth impairment and FCR born  $< 35$  weeks were affected by a further -0.76 SD. FCR, for those born  $< 35$  weeks of gestation, was associated with increased deficit in cognition, and with prolonged VEP latencies.

### **2.3.5 Sex-specific effects**

Effects of sex were specifically examined in 4 of the 38 papers included (10.5%), 2 in the  $\geq 35$  weeks of gestation group, and 2 in the  $< 35$  weeks of gestation group. These papers had mixed results. In the  $\geq 35$  weeks of gestation group, one paper showed a specific effect in females, such that females with fetal growth impairment performed worse on a multidimensional neurodevelopment test (assessing cognition, attention and executive function), compared to males with fetal growth impairment<sup>43</sup>. The second paper, however, showed a specific effect in males, such that male sex and abnormal Doppler indices together conferred an increased risk for motor dysfunction in childhood<sup>39</sup>.

In the  $< 35$  weeks of gestation group, one paper found no modification effect of sex on the association between HC growth and cognition at 2 years of age<sup>68</sup>, whereas another



separated analyses by sex, and found that a specific effect in males, such that preterm males with fetal growth impairment had poorer cognitive outcomes compared to preterm males without fetal growth impairment<sup>64</sup>. A further 8 papers (four  $\geq 35$  weeks and four  $< 35$  weeks) adjusted their findings for sex, but did not specifically examine sex differences.

### **2.3.6 Co-occurrences of neurodevelopmental impairment in multiple domains**

Thirteen papers examined the effects of fetal growth impairment across multiple domains in children born  $\geq 35$  weeks of gestation, allowing assessment for the presence of co-occurring disturbances (impairment occurring in two domains simultaneously; Figure 2.6). The most common co-occurrences were between cognitive and behavioural deficits, hearing and language deficits, and behavioural and motor deficits, in children born at  $\geq 35$  weeks of gestation. These co-occurrences were identified in 100% of studies that examined these domains concurrently. The cognitive domain was identified as having the largest number of co-occurring deficits, with growth impaired children with cognitive deficits also likely to exhibit behavioural, language and motor problems. No studies examined the effects on vision concurrently with any of the other domains.

Generally, a larger number of the  $< 35$  weeks of gestation papers examined the outcomes of fetal growth impairment across multiple domains, compared to those in the  $\geq 35$  week group. The most common co-occurrences in children born  $< 35$  weeks of gestation with fetal growth impairment were between visual and behavioural deficits and visual and cognitive deficits. These co-occurrences were identified in 100% of studies that examined both these domains. The visual domain was identified as having the largest number of co-occurrences, with co-occurring deficits also identified in behavioural, language, motor, cognitive and hearing development. Overall a higher number of co-occurrences were identified in the follow-ups of children born  $< 35$  weeks of gestation with fetal growth impairment.

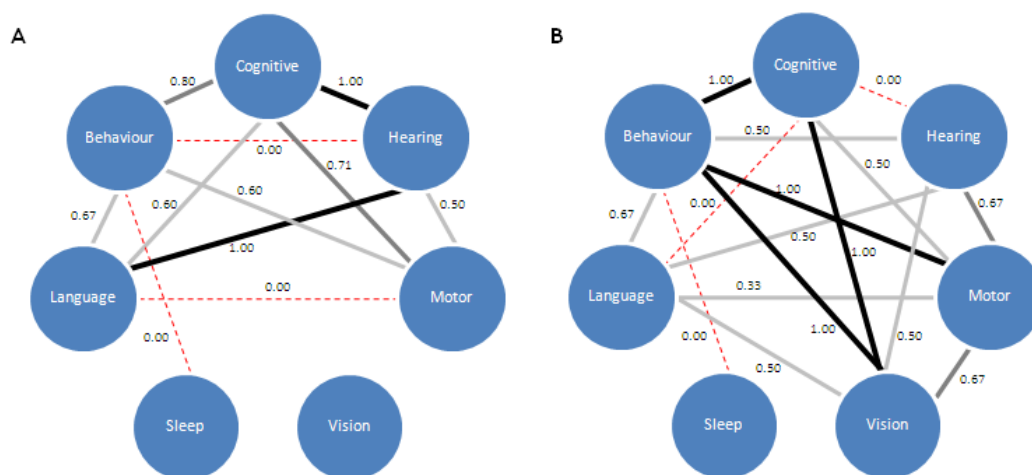


**Figure 2.6.** Co-occurrences identified in the neurodevelopmental outcomes of neonates born  $\geq 35$  weeks with fetal growth impairment (A). Co-occurrences identified in the neurodevelopmental outcomes of neonates born  $< 35$  weeks with fetal growth impairment (B). Numbers presented represent the number of studies that identified a co-occurrence of outcomes, compared to the total number of studies that examined that co-occurrence (Proportion = Number of identified co-occurrences/total number of studies examining that co-occurrence). Darker lines indicate a greater proportion of identified co-occurrences. Black thick lines indicate that all studies (100%) examining that co-occurrence identified co-occurrence. Red dotted lines indicate that none of the studies examining that co-occurrence identified co-occurrences. No line between domains indicates that no study has examined these outcomes together.

## 2.4 Summary of results

The aim of this systematic review was to assess the effects of impaired fetal growth on a range of neurodevelopmental outcomes in childhood, and to examine whether the outcomes of growth impairment differ in children born  $\geq 35$  weeks of gestation and  $< 35$  weeks of gestation. Overall, fetal growth impairment was associated with poorer long-term outcomes in a number of neurodevelopmental domains, most clearly, behavioural (SMD=0.74), and cognitive development (SMD=0.71). Separating out the gestational age groups, in children born  $\geq 35$  weeks of gestation, fetal growth impairment was most clearly associated with behaviour (SMD=0.47), cognitive development (SMD=0.52) and vision (SMD=0.83). In children born  $< 35$  weeks

gestation, fetal growth impairment was most clearly associated with poorer outcomes in behavioural (SMD=1.00), cognitive development (SMD=0.89) and hearing function (SMD=0.96). In studies examining children born  $\geq 35$  weeks of gestation, fetal growth impairment was associated with an approximate 0.5 SD deficit across neurodevelopmental domains. In the studies of children born  $< 35$  weeks of gestation, fetal growth impairment was associated with an approximate 0.7 SD deficit across all neurodevelopmental domains.

Stunting and wasting indices at birth had stronger associations with neurodevelopment than BW indices measures in both GA groups. In children born  $\geq 35$  weeks, stunting showed the strongest association with poor neurodevelopmental outcomes, and in children born  $< 35$  weeks gestation, wasting showed the strongest association with poor neurodevelopmental outcomes. This indicates that LBW, as an indicator of impaired fetal growth, is a less effective predictor of poor neurodevelopmental outcomes than measures that capture the specific growth phenotype. Further research in larger samples (such as in large, prospective birth cohort studies) would be useful to validate this finding.

FCR was associated with greater risk of neurodevelopmental deficit, particularly in behavioural and cognitive development in children born  $\geq 35$  weeks and  $< 35$  weeks of gestation. FCR was also demonstrated to lead to prolonged VEP latencies in children in both GA groups, possibly indicating delayed neural myelination. Importantly, contrary to popular understanding, FCR was not demonstrated to result in neuroprotective effects. The studies included in this review suggest that FCR confers an additional 0.5 SD deficit on the neurodevelopment of growth impaired neonates. This indicates that FCR may be a marker of a more severe form of growth impairment, and does not have protective effects for growth impaired neonates.

Sex-specific differences were examined in 4 of the 38 studies (10.5%). The results of these were mixed, with one study in the  $\geq 35$  weeks of gestation finding a specific effect for females (cognitive outcomes), and one for males (motor outcomes). In the  $< 35$  weeks of

gestation group, one study found a specific effect for males, and one found no differences between males and females (both cognitive outcomes). Potential sex-specific effects require further exploration, and will be examined further in Chapter 7.

Growth impaired children born at <35 weeks GA were identified as being more likely to have co-occurring deficits across multiple domains than those born  $\geq 35$  weeks of gestation. This indicates that prematurity confers a greater risk for poor neurodevelopmental outcome across a number of concurrent domains, rather than in singular domains. Further study, however, is needed to validate this finding, as it is possible that the higher number of co-occurrences in infants born <35 weeks may be because more studies have conducted follow-ups in multiple domains in this group.

#### **2.4.1 Behavioural development**

The vast majority of studies examining the behavioural outcomes of fetal growth impairment identified significant deficits in behavioural development during childhood. This outcome was also identified, albeit less so, in growth impaired children born <35 weeks. The behavioural domain most commonly affected was attention (identified most commonly by parent-report on behavioural questionnaires), followed by difficulties in personal-social, adaptive, hyperactivity and internalising behaviour.

#### **2.4.2 Cognitive development**

The results of the current review identified some interesting patterns in the cognitive development of children with fetal growth impairment. In children born  $\geq 35$  weeks of gestation, fetal growth impairment was identified to have a small, but significant negative impact on cognitive development, across a range of cognitive and executive functions, including memory, spatial abilities, problem solving and global cognitive function.

Whilst children with fetal growth impairment had poorer cognitive outcomes compared to normally grown children, their cognitive abilities were still in the normal range. This, however,

was not the case in children born at <35 weeks of gestation with fetal growth impairment, who showed greater neurodevelopmental deficits than those that were growth impaired but born at a later GA. This may suggest that neonates with preterm birth *and* fetal growth impairment have an increased risk for later cognitive deficits, compared to those born with fetal growth impairment but at full or near-to-full term.

### **2.4.3 Language development**

The studies examining the effect of fetal growth impairment on language development had mixed results, suggesting that the relationship between fetal growth and language development during childhood may have greater complexity than some other neurodevelopmental outcomes. A hypothesised reason for the inconsistent results may be the heterogeneity of language competencies assessed at follow-up, with assessments conducted in a range of vocabulary, verbal problem solving, expressive and receptive communication abilities. It is possible that fetal growth impairment exerts differential effects across language abilities, and thus aggregating language outcomes dilutes any identifiable effects. Alternatively, it may be that language development is not specifically affected by fetal growth impairment, but rather that any identifiable differences in language abilities of children with fetal growth impairment may be reflective of broader cognitive, behavioural and sensory deficits. The results of the current review identified language deficits to be most often associated with hearing and behavioural deficits.

Similarly to cognitive development, no effect of fetal growth impairment on language competency was identified prior to 18 months of age. This most likely reflects the time course of development of language in toddlers, before which, language deficit would be difficult to detect.

#### **2.4.4 Motor development**

The current review identified fetal growth impairment to affect both gross and fine motor development in childhood. This impairment was identifiable from 8 weeks post-birth, and remained present and stable throughout childhood. This finding provides support for theories suggesting that motor dysfunction may be identifiable from birth<sup>2</sup>. Interestingly, the timing of onset of fetal growth impairment appeared to differentially affect the specific aspect of motor development that was affected. Overall, there was a greater level of motor disturbance when growth impairment occurred during early gestation. The rate of growth in early-mid pregnancy was positively associated with both gross and fine motor development in childhood<sup>5</sup>; however the rate of growth in mid-late pregnancy was associated with gross motor development outcomes only<sup>4</sup>.

An unexpected finding was that although a clear association between fetal growth impairment and motor deficits was identified in those born  $\geq 35$  weeks of gestation, the results were more inconsistent in children born  $< 35$  weeks of gestation. This is in contrast to previous findings that have identified preterm birth to be predominantly associated with motor dysfunction<sup>73,74</sup>, and to a lesser degree, cognitive deficits<sup>38</sup>. As such, this finding requires further exploration to identify the separate and concurrent effects of preterm birth and fetal growth impairment on motor development.

#### **2.4.5 Vision development**

All studies of visual function in children with fetal growth impairment identified some form of visual dysfunction, including prolonged VEP latencies, impaired general visual responses, a higher prevalence of occlusion-related visual disturbances, and a higher likelihood of severe acuity loss. The single study of visual function in children born  $\geq 35$  weeks of gestation identified prolonged VEP latencies<sup>47</sup>. This same pattern of change in VEPs was identified in children that were born at  $< 35$  weeks of gestation with fetal growth impairment. This suggests that fetal

growth impairment may have a characteristic effect on the latencies of VEPs, regardless of GA at birth. Variations in VEPs in growth impaired fetuses have been shown to be identifiable from birth<sup>41</sup>, and have been suggested to be potentially indicative of delayed brain maturation and delayed neuronal myelination.

#### **2.4.6 Hearing development**

The results of the studies on the effect of fetal growth impairment on auditory function were mixed. The single study of hearing deficit in children born at  $\geq 35$  weeks of gestation, showed no effect of fetal growth impairment on hearing, whereas the majority of studies in children born at  $< 35$  weeks of gestation identified fetal growth impairment to have a negative effect on hearing ability. One potential reason for these mixed results may be that the teratogens that lead to growth impairment in utero (such as infection during pregnancy)<sup>75</sup> have also been shown to lead to auditory dysfunction. As such, fetal growth impairment and auditory dysfunction may be concurrent effects of a compromised intrauterine environment.

#### **2.4.7 Sleep development**

Despite the importance of the role of sleep in child neurodevelopment<sup>76-78</sup>, studies examining the effect of fetal growth impairment on sleep outcomes in childhood have been very limited. The current review identified only one study that examined the effect of fetal growth impairment on sleep in children at 4-7 years of age. The primary effect identified was that children with fetal growth impairment had less true sleep time, possibly reflective of less time spent in bed. This neurodevelopmental domain requires much further research.

### **2.5 Strengths and limitations of systematic review**

This review has a number of unique features: 1) it is a detailed examination of the effect of stringently defined fetal growth impairment on disaggregated neurodevelopmental outcomes; 2) studies have been separated based on GA at birth to allow examination of the potential additive effects of preterm birth; and 3) studies have been pooled to examine the

specific effects of different growth phenotypes at birth (stunting and wasting compared to BW measures), and the specific effects of FCR.

However, the review does have limitations due to the heterogeneity of: 1) the methods used to identify growth impairment, including the growth charts used; 2) the control groups selected; and 3) the follow-up assessments. In regards to heterogeneity of growth impairment identification methods, fetal growth impairment was confirmed using both serial ultrasound, that identifies the time-of-onset of growth restriction, and Doppler velocimetry, which provides information about relative perfusion and extent of placental vascular resistance. Furthermore, in utero identification of fetal growth impairment was confirmed by anthropometric measures at birth. Including both methods of identifying growth restriction in utero (serial ultrasound and Doppler velocimetry) allowed the current review to obtain an adequate sample of studies from which conclusions could be reliably drawn.

Another potential limitation is that the follow-up studies were included only up to the beginning of adolescence. This upper limit was chosen as the onset of puberty signifies the point after which trajectories of brain development remain relatively stable<sup>79</sup>, however it also possible that neurodevelopmental deficit that was not identified in childhood may become evident in adolescence (as has been identified in cases of stimulant<sup>81,81</sup> and early stress exposure<sup>82</sup>).

A further limitation of the current systematic review is that the search, paper selection, quality rating and data extraction was conducted by a single researcher. This potential source of bias must be considered when interpreting results.

## **2.6 Conclusions**

The primary aim of this systematic review was to examine the overall effect of fetal growth impairment on neurodevelopment in childhood. The secondary aims were to 1) identify any differential effects of fetal growth impairment across neurodevelopmental domains; and 2)



identify any differential effects of heterogeneous growth phenotypes (stunting, wasting and BW indices). Overall, fetal growth impairment was associated with a 0.5 SD neurodevelopmental deficit in childhood, with an additional 0.2 SD deficit in children born <35 weeks of gestation. Disaggregation by neurodevelopmental domain revealed fetal growth impairment was particularly associated with poor cognitive, and behavioural (specifically attention) development. Inconsistent effects were identified in motor, hearing, language and sleep development. Stunting and wasting were associated with greater neurodevelopment impairment, compared to confirmation of impaired fetal growth by BW indices.

Based on these findings, this thesis will focus specifically on attention and cognitive outcomes in childhood, as these domains showed the strongest associations with poor fetal growth, compared to the other domains. To examine potential differences in the outcomes associated with different growth phenotypes, indices of BW, stunting, wasting and asymmetry will be examined separately. Potential sex-specific effects will also be examined. For the remainder of this thesis, fetal growth impairment will be assessed only by anthropometric indices taken at birth (as fetal measurements across all three birth cohorts are not available).

## 2.7 References

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## **3 General methodology**

### **Chapter outline**

#### **3.1 Pelotas 2004 Birth Cohort Study (Pelotas)**

3.1.1 Research setting and sample

3.1.2 Primary measures

3.1.3 Confounding variables

#### **3.3 Avon Longitudinal Study of Parents and Children (ALSPAC)**

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3.2.2 Primary measures

3.2.3 Confounding variables

#### **3.3 International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century (INTERGROWTH-21<sup>st</sup>)**

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#### **3.4 Calculation of birth anthropometric indices across all three cohorts**

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#### **3.8 Summary**

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This chapter includes a detailed description of the methodology of this thesis. The overarching aim of this thesis is to examine the association between impaired fetal growth, measured by anthropometric indices at birth, and attention and cognitive outcomes in childhood. To answer this question, three longitudinal prospective cohorts have been studied: the 2004 Pelotas Birth Cohort<sup>1</sup>, the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort<sup>2</sup>, and the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) Project cohort<sup>3</sup>.

The use of multiple cohorts to examine the research questions allows inferences to be made about the cross-cultural validity and robustness of results across populations with different confounding structures. The 2004 Pelotas Birth Cohort was drawn from Pelotas, Brazil (an upper-middle-income country according to the 2015 World Bank classification<sup>4</sup>), and is a descriptive sample consisting of mothers at high- and low-risk of impaired fetal growth (i.e. no specifications of demographic or health requirements for entry to the study). The ALSPAC cohort was drawn from three health districts in the southwest of England, UK (a high-income country<sup>4</sup>), and is also a descriptive sample with no demographic or health specification for entry to the study. The third cohort is a sample from the INTERGROWTH-21<sup>st</sup> Project, which consists of mothers and children from five diverse geographical locations. These include the United Kingdom, Italy (both high-income countries<sup>4</sup>), Brazil (an upper-middle-income country<sup>4</sup>), India (a lower-middle income country<sup>4</sup>) and Kenya (a low-income country<sup>4</sup>). Mothers included in the INTERGROWTH-21<sup>st</sup> project, a prescriptive sample, were specifically recruited as being at low-risk for impaired fetal growth. This is because creating a set of optimal growth standards was the primary aim of the INTERGROWTH-21<sup>st</sup> Project. Including the INTERGROWTH-21<sup>st</sup> cohort allowed examination of whether the association between fetal growth and neurodevelopment endures in mothers that are at low-risk for impaired fetal growth, and also allows comparison across high-, middle- and low-income samples when potential confounding structures are held constant.



This chapter presents the general methodology used in the three cohorts, including research setting, participant recruitment, birth anthropometric measurement methods, follow-up assessments, neurodevelopmental assessment tools, and collection of data regarding potential confounding variables. Finally, the chapter includes an *a priori* sample size estimation (used to determine the suitability of sample sizes to answer the research questions), a rationale of the scope of this research, and the methodological strengths and limitations. Specific details regarding sample sizes included in particular analyses are presented in results chapters 5-7.

### **3.1 Pelotas 2004 Birth Cohort Study (Pelotas)**

#### **3.1.1 Research setting and sample**

The 2004 Pelotas Birth Cohort was drawn from a population of children born in 2004, in Pelotas, located in the Brazilian state of Rio Grande do Sul (Figure 3.1). Pelotas has approximately 340,000 inhabitants, and the major economic activities are agriculture (predominantly rice cultivation and cattle farming), and services, including two universities. All mothers giving birth during 2004, who resided in the urban area of Pelotas or in the adjacent neighbourhood of Jardim América (part of the municipality of Capão do Leão), were approached for recruitment and interviewed within 24 hours of delivery. Children were followed up at ages 3, 12, 24 and 48 months. The study protocol was approved by the Medical Ethics Committee of the Federal University of Pelotas, affiliated with the Brazilian Federal Medical Council. Written informed consent was obtained at each follow-up assessment from women prior to participation in the study. A detailed description of the 2004 Pelotas birth cohort is given elsewhere<sup>1,5</sup>.



**Figure 3.1. Location of Pelotas, Brazil; H=Hospital locations<sup>6</sup>**

### **3.1.2 Primary measures**

#### **3.1.2.1 Obstetric measurements**

##### **3.1.2.1.1 Birth anthropometric assessment**

Maternity staff weighed neonates. Other anthropometric measurements were taken by a trained and supervised study researcher at the time of birth. Two measurements were conducted for accuracy of measurements, by one assessor. Measurement was considered valid when both measurements were in agreement. Neonates were weighed using regularly calibrated pediatric scales, and length measurements were taken in supine position using Appropriate Health Resources and Technologies Action Group (AHRTAG) infantometers with 1mm precision. Head circumference (HC) and abdominal circumference (AC) were measured by standardized tape measure. Gestational age (GA) was estimated using the algorithm proposed

by the National Center for Health Statistics (NCHS)<sup>7</sup>, based on the last menstrual period (LMP), when consistent with birth weight (BW), birth length (BL) and HC<sup>8</sup>. If inconsistencies were identified, or if the date of last menstrual period was unknown, then GA was determined by clinical maturity estimate, based on the Dubowitz method<sup>9</sup>. Further information on the calculation of birth anthropometric indices is presented in section 3.4.

### **3.1.2.2 Follow-up assessment**

#### **3.1.2.2.1 The Child Behaviour Checklist (CBCL)**

Child attention was assessed at 4 years of age using the Attention Problems Syndrome Scale of the Child Behaviour Checklist (CBCL) 4-18<sup>10</sup>, by trained interviewers (Appendix III). The CBCL is a widely used parent-report questionnaire, which has demonstrated ability to identify behavioural problems in childhood<sup>11</sup> and has been validated in Brazilian children<sup>12</sup>. It has demonstrated validity in identifying children with attention impairments, with the Attention Problems Syndrome Scale demonstrating good test-retest reliability ( $r=0.92$ ), good inter-rater reliability ( $r=0.73$ ), and good internal consistency ( $\alpha=0.75$ )<sup>13</sup>. The items on the CBCL are rated on a three-point ordinal scale by the parent or teacher (0 = not true; 1 = somewhat or sometimes true; 2 = very true or often true).

All attention ratings were completed by the mother in the 2004 Pelotas Birth Cohort. The assessment was conducted by trained interviewers, in interview format, which is accepted by the instrument's authors as a valid administration technique. Interview was selected as the means of administration to prevent error among mothers with low literacy skills. The attention items were administered as part of the full CBCL questionnaire.

#### **3.1.2.2.2 The Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R)**

The Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R)<sup>14</sup> was administered to children at 4 years of age. The WPPSI-R is a widely-used, individually administered cognitive assessment for children aged from 30 months to 7 years 3 months. The

WPPSI comprises 10 subtests, 5 verbal and 5 performance. The verbal subtest raw scores are scaled to make up the *verbal IQ* (VIQ) and the performance scores scaled to make up the *performance IQ* (PIQ). The 10 subtest scores together are scaled to produce a full-scale IQ score (FSIQ), which is defined as an average of all cognitive abilities, and is standardized at  $M=100$ ,  $SD=15$ . The WPPSI-R has good test-retest reliability ( $r=0.90$ )<sup>15</sup>, inter-rater reliability ( $r=0.82$ )<sup>16</sup>, good internal consistency ( $\alpha=0.97$ )<sup>17</sup> and stability of factor structure<sup>18</sup>. Furthermore, the WPPSI-R FSIQ score has been shown to have good long-term predictive validity for educational achievement and overall grade point averages in adolescence<sup>19</sup>.

An abbreviated version of the WPPSI-R has been developed and standardized, which consists of 4 subsets (picture completion and block design (comprising PIQ), and comprehension and arithmetic (comprising VIQ))<sup>20</sup>. Similarly to the full WPPSI-R, these scores combine to produce a full-scale FSIQ ( $M=100$ ,  $SD=15$ ). The abbreviated version has strong concurrent validity with the full WPPSI-R ( $r=0.92$ )<sup>20</sup>. This abbreviated version has been adapted to Portuguese<sup>21</sup>, and has been validated to Argentinian standards<sup>22</sup> (although not yet in Brazil). The WPPSI-R was administered in the 2004 Pelotas Birth Cohort by a trained psychologist, during a home visit.

### **3.1.3 Confounding variables**

Data on maternal age, maternal skin colour as identified by the interviewer (black, white or other), maternal BMI, maternal smoking during pregnancy, maternal alcohol consumption during pregnancy, marital status, maternal schooling, family income, and maternal health during pregnancy (physical and mental), were collected in the perinatal interview (Appendix IV). Family wealth at birth was classified into quintiles using asset indices, based on principal components analysis of domestic item ownership (e.g. household appliances, car etc.) and characteristics of the residence (e.g. number of bathrooms and bedrooms<sup>23</sup>). This is in accordance with convention for analyses using this cohort. Single, divorced, widowed, or women living without a

partner were classified as single mothers. Maternal skin colour was categorised as black, white, or other, based on interviewer classification. Parity was defined as the number of previous viable pregnancies. Maternal smoking habits, alcohol consumption, physical and mental health during pregnancy were based on maternal report, and assessed retrospectively at birth. Child characteristics collected in the perinatal interview included data on sex of the child, mode of delivery, multiple birth and APGAR scores<sup>24</sup> at 1 and 5 minutes.

Data regarding hospitalisation during the first 3 months was collected at the 3 month follow-up (Appendix V). Child size at 24 months was measured by interviewers trained in anthropometric techniques, at the 24 month follow-up. Tanita electronic scales (Tanita, Tokyo, Japan), calibrated weekly with 100g precision, were used to assess weight. Child length was measured in supine position using portable ARTHAG infantometers with 1mm precision. Growth indicators (height-for-age and weight-for-height Z-scores) were calculated based on the WHO growth curves<sup>25</sup>, using Anthro 2005 software<sup>26</sup>. Presence of neurological illness (the presence of convulsion without fever or meningitis) was assessed in the 48 month follow-up (Appendix VI). Duration of breastfeeding was assessed in all follow-up sessions, and the earliest available information regarding duration of breastfeeding was used to reduce recall bias.

## **3.2 Avon Longitudinal Study of Parents and Children (ALSPAC)**

### **3.2.1 Research setting and sample**

This study was conducted in women with an expected delivery date between 1<sup>st</sup> April 1991 and 31<sup>st</sup> December 1992, in three health districts in the southwest of England (Bristol and Weston, Frenchay and Southmead District Health Authorities; Figure 3.2).

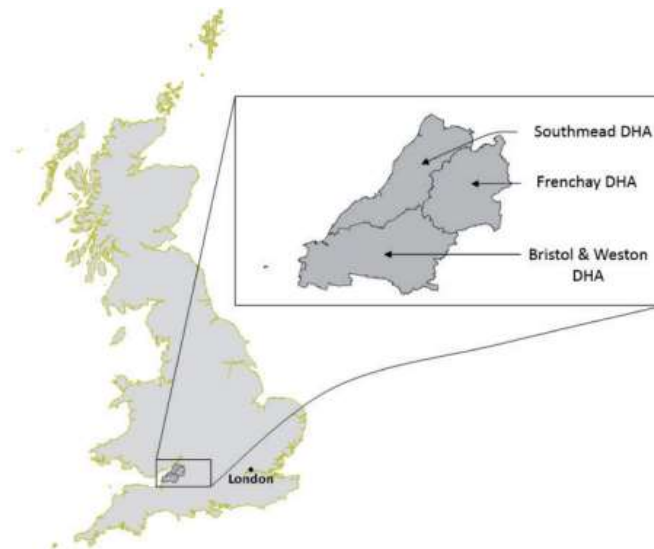


**Figure 3.2. The ALSPAC study area within the UK and details illustrating the three eligible NHS District Health Authorities (DHAs)<sup>27</sup>**

A total of 14,541 children were recruited for the ALSPAC study, and were interviewed within 24 hours of delivery. Children were followed-up at multiple time-points, and cognitive and attention assessments were conducted at 4 and 6 years of age, respectively. The recruitment flow-chart is presented in Figure 3.3. Further description of the ALSPAC cohort is given elsewhere<sup>27</sup>.

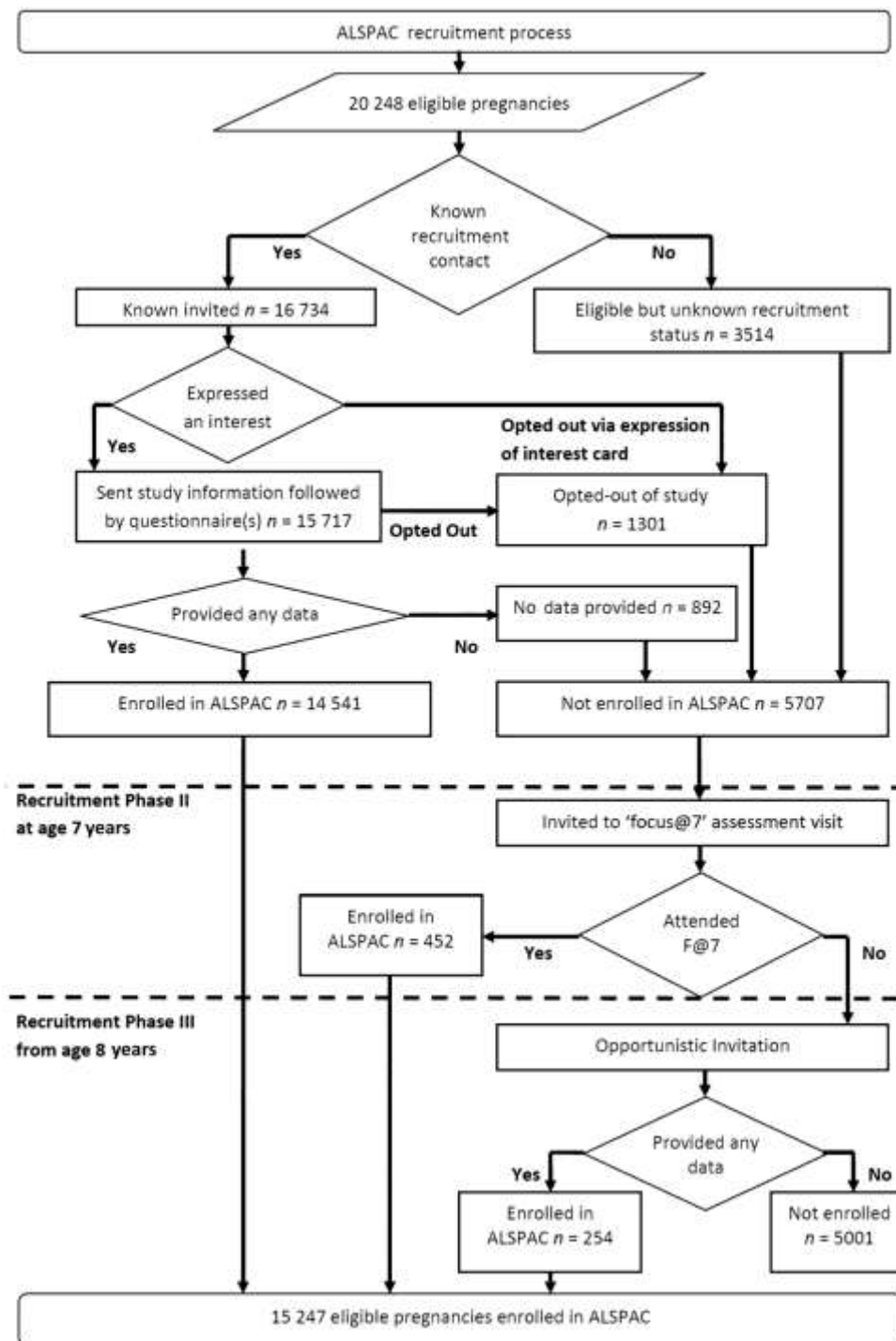


Figure 3.3. ALSPAC recruitment flow-chart

### **3.2.2 Primary measures**

#### **3.2.2.1 Birth anthropometric measurements**

BW was recorded from obstetric data and from central birth notification data. Where values disagreed by <100 g then the lowest value was accepted; if the values disagreed by >100 g then the value was coded as missing. HC and BL (crown-to-heel) were measured using a Holtain neonatometer (Holtain Ltd., Crymlych, Wales) by trained ALSPAC staff who visited all study participants within 24 hours of birth where the mother gave permission. If these values were missing, the values were extracted from the medical records by trained study staff. GA was measured from the date of the LMP, provided it was in agreement with the results of the dating ultrasound scan (<20 weeks). In case of a discrepancy between the stated date of the LMP and the date identified by ultrasound, estimation was made by an experienced obstetrician. Information on the calculation of birth anthropometric indices is presented in section 3.4.

#### **3.2.2.2 Follow-up assessments**

##### **3.2.2.2.1 The Strengths and Difficulties Questionnaire**

The Strengths and Difficulties Questionnaire (SDQ) was administered to parents of children, when children were 6-7 years of age, with the hyperactivity/inattention subscale used to assess child attention function. The SDQ is a brief behavioural screening questionnaire for children aged 3-16 years, which consists of 5 subscales, including emotional problems, hyperactivity, relationship, conduct and pro-social behaviour<sup>28</sup> (Appendix VII). The SDQ is an extensively evaluated parent-report tool<sup>29</sup>, with good test-retest reliability ( $r=0.71$ ), moderate-good inter-rater reliability ( $r=0.47$ ) and good internal consistency ( $\alpha=0.76$ )<sup>30</sup>. It has been shown to be a valid assessment of child behavioural problems<sup>31</sup>. The concurrent validity between the attention ratings of the SDQ and the CBCL has been shown to be high ( $r=0.75$ )<sup>32</sup>, and the similarity between these two assessments is consistent across sexes<sup>33</sup>. The SDQ items are rated on a three-point ordinal scale (0 = not true; 1 = somewhat true; 2 = certainly true).



#### 3.2.2.2.2 The Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R)

All scales of the WPPSI-R<sup>34</sup> were administered when the child was approximately 4 years old, by a trained psychologist in a clinic-based testing session, which lasted approximately 50-60 minutes. In order to calculate the VIQ, PIQ and FSIQ, at least eight subtests (4 verbal, 4 performance) had to be completed. From these scores, the missing data could be imputed such that the final score could be calculated. This prorating is standard practice for the WPPSI<sup>34</sup>, and allows some calculation of values in cases of missing data. Further information on the structure and psychometric properties of the WPPSI-R are presented in section 3.1.2.2.2.

#### 3.2.3 Confounding variables

Data on potential confounders were collected in self-report postal questionnaires completed by the mother during pregnancy (Appendix VIII) or in the neonatal period (Appendix IX). Early pregnancy maternal age, height and weight was measured by self-report, and was collected at approximately 12 weeks gestation. Demographic data on maternal education (none/Certificate of Secondary Education [CSE]; vocational; O level [national school exams at 16 years]; A level [national school exams at 18 years]; or university degree), occupation (which was used to classify them into social categories according to the 1991 Office and Populations Censuses and Surveys Standard: [I-V, where I is the highest category (professional) and V is the lowest category (unskilled manual worker)<sup>35</sup>, marital status (never married; widowed; divorced; separated; married once only; married for a second or third time) and ethnicity (white; black/Caribbean; black/African; black/other; Indian; Pakistani; Bangladeshi; Chinese; other), and gestational data on maternal depression (Edinburgh Postnatal Depression Scale; EPDS)<sup>36</sup>, smoking and alcohol consumption, and hypertension and diabetes during pregnancy was collected at 32 weeks gestation. Obstetric information regarding mode of delivery, APGAR score at 5 minutes, and admission to neonatal intensive care was collected from obstetric records at birth. Weekly family income was assessed by questionnaire at 47 months postnatally (five categories: <£100; £100-199; £200-299; £300-399; >£400 per week). Information was collected

at 12 months postnatally regarding length of breastfeeding, and categorised into three categories (never;  $\leq 6$  months;  $> 6$  months) .

### **3.3 International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century (INTERGROWTH-21<sup>st</sup>)**

#### **3.3.1 Research setting and samples**

The International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century (INTERGROWTH-21<sup>st</sup>) is a large-scale, population-based, multicentre project involving health institutions from 8 geographically diverse countries, including Brazil, China, India, Italy, Kenya, Oman, UK and USA. The conception of the INTERGROWTH-21<sup>st</sup> Project was based on the belief that growth in utero is influenced by genes and parental constitution, in addition to environmental factors such as nutrition, smoking and maternal illnesses. To reduce heterogeneity in the cohort introduced by these factors, important variables in the cohort have been rigorously standardised.

The aggregation of data drawn from multiple local datasets into a single cohort, is supported by observations that ethnic differences contribute only a small part (approximately 3%) of the total variation in growth among well-nourished children; most of the variance is related to environmental conditions such as health, nutrition, and socio-demographic factors. These variables were held constant, as much as possible, reflected in the INTERGROWTH-21<sup>st</sup> inclusion and exclusion criteria. As such, the design of the INTERGROWTH-21<sup>st</sup> Project is to examine all infants as a single cohort.

In acknowledgement of these considerations, the current thesis in the first instance will examine the INTERGROWTH-21<sup>st</sup> cohort as a single cohort (in accordance with the INTERGROWTH-21<sup>st</sup> Project original conceptualisation and design). Following this, however, to examine potential cross-site differences, a second analysis will be conducted, repeating the aggregated analyses but disaggregating the INTERGROWTH-21<sup>st</sup> cohort by site.

The INTERGROWTH Neurodevelopmental Assessment (INTER-NDA) was developed to assess neurodevelopment at 2 years of age across 5 of the 8 sites (Brazil, United Kingdom, Italy, Kenya and India). These sites were chosen to achieve geographical distribution across continents, and previous participation in perinatal health randomized controlled trials and/or multicentre observational studies were considered advantageous.

Institutions within the geographical regions were selected on the basis that they served low-risk populations based on locally adapted definitions, and were able to provide the number of participants required (>1000 births per institution per year). Locally defined constructs of socio-economic characteristics that posed low-risk for growth constraints included a combination of measures of household income, housing tenure, education, occupation and employment status<sup>3</sup>. In addition, the institutions had to have a low rate of LBW (<10%) and a mean BW greater than 3100g, be located at an altitude of less than 1600m, have a perinatal mortality rate of less than 20 per 1000 live births, and an absence of known non-microbiological contamination (e.g. pollution, radiation or any other toxic substance). The recruitment flow-chart is presented in Figure 3.4. As data were frozen for analysis in the current thesis, a total of 1076 infants were outside the age of eligibility at the time of assessment, leaving 1649 eligible for assessment with the INTER-NDA.

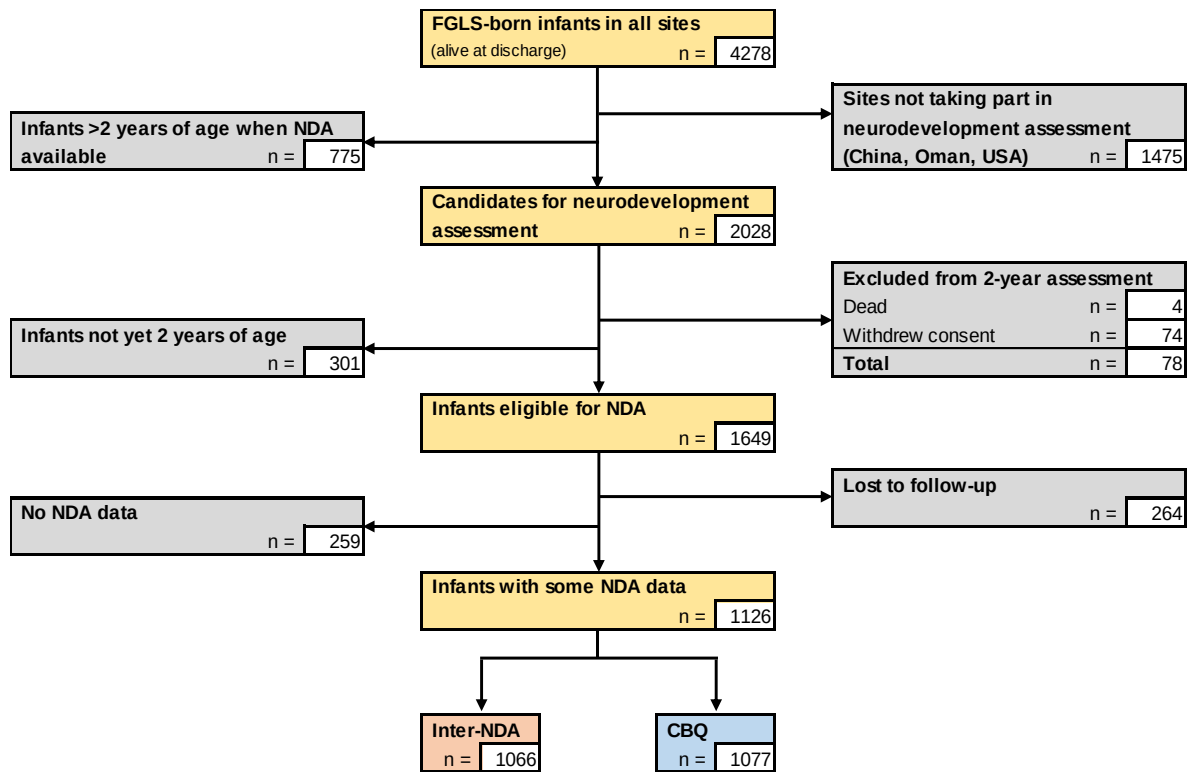


**Figure 3.4. Postnatal infant follow-up study subjects flow-chart. FGLS=Fetal growth longitudinal study; NDA=neurodevelopmental assessment; CBQ=Child Behaviour Questionnaire.**

Specific inclusion criteria for mothers in the INTERGROWTH-21<sup>st</sup> Project are presented below. Women were selected on the basis of posing low-risk for preterm delivery and intrauterine growth restriction (IUGR). Whilst there are numerous risk factors for these outcomes, the selection criteria used for INTERGROWTH-21<sup>st</sup> were based on those that were have been commonly identified by systematic reviews<sup>37-39</sup> and are generally accepted by the medical community. Inclusion criteria for women recruited to the INTERGROWTH-21<sup>st</sup> study are presented in Figure 3.5

- a) aged  $\geq 18$  and  $< 35$  years;
- b) BMI  $\geq 18.5$  and  $< 30$  kg/m<sup>2</sup>;
- c) height  $\geq 153$  cm;
- d) singleton pregnancy;
- e) a known LMP with regular cycles (defined as 28 days  $\pm$  4 days) without hormonal contraceptive use, or breastfeeding in the 2 months before pregnancy;
- f) natural conception
- g) no relevant past medical history (refer to screening form), with no need for long-term medication (including fertility treatment and over-the-counter medicines, but excluding routine iron, folate, calcium, iodine or multivitamin supplements);
- h) no evidence of socio-economic constraints likely to impede fetal growth identified using local definitions of social risk;
- i) no use of tobacco or recreational drugs such as cannabis in the 3 months before or after becoming pregnant;
- j) no heavy alcohol use (defined as  $> 5$  units (50ml pure alcohol) per week) since becoming pregnant;
- k) no more than one miscarriage in the 2 previous consecutive pregnancies;
- l) no previous baby delivered pre-term ( $< 37$  weeks) or with a birth weight  $< 2500$ g or  $> 4500$ g;
- m) no previous neonatal or fetal death, previous baby with any congenital malformations, and no evidence in present pregnancy of congenital disease or fetal anomaly;
- n) no previous pregnancy affected by pre-eclampsia/eclampsia, HELLP syndrome or a related pregnancy-associated condition;
- o) no clinically significant atypical red cell alloantibodies;
- p) negative urinalysis;
- q) systolic blood pressure  $< 140$  mmHg and diastolic blood pressure  $< 90$  mmHg;
- r) no diagnosis or treatment for anaemia during this pregnancy (Hb levels will be monitored throughout pregnancy)
- s) no clinical evidence of any other sexually transmitted diseases, including syphilis and clinical Trichomoniasis;
- t) not in an occupation with risk of exposure to chemicals or toxic substances, or very physically demanding activity to be evaluated by local standards. Also women should not be conducting vigorous or contact sports. as well as scuba diving or similar activities

**Figure 3.5. Inclusion criteria for women recruited to the INTERGROWTH-21<sup>st</sup> study<sup>3</sup>**

### United Kingdom

The city of Oxford in the United Kingdom was chosen as one of two European INTERGROWTH-21<sup>st</sup> sites. Oxford is located in the county of Oxfordshire, in south-central region of England (Figure 3.6).

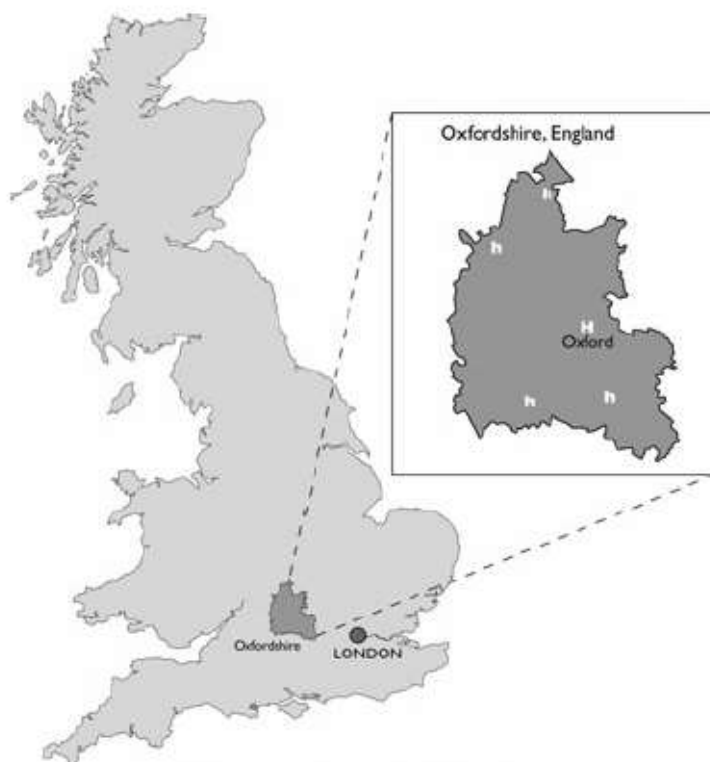


**Figure 3.6. Location of Oxford, United Kingdom. H = hospital participating in the INTERGROWTH-21st Project<sup>40</sup>**

Oxfordshire has a population of 639,700 inhabitants, a large proportion of which are young, middle-class, well-educated, professional families, with a GDP per capita of approximately £22,624 (US\$38,405)<sup>41</sup>. The population of Oxford city is approximately 150,000, and the main economic activities are services (including tourism, retail and two universities) and car manufacturing. The John Radcliffe Hospital (which covers 75.3% of deliveries in Oxfordshire) was the main maternity unit selected to enroll mothers into the INTERGROWTH-21<sup>st</sup> study and as the Project Coordinating Unit. Ninety-nine percent of mothers delivering at the John Radcliffe Hospital are educated to secondary-school or university-level. The prevalence of LBW is 6%, with a mean BW of 3334g (Table 3.1). The site-specific socio-economic cut-off was defined as women not receiving income support benefit or job-seekers allowance.

### 3.3.1.1 Italy

Turin, located in the Piemonte region of Northern Italy, was selected as one of two European sites for INTERGROWTH-21<sup>st</sup> (Figure 3.7).



**Figure 3.7. Location of Turin, Italy. H = hospital participating in the INTERGROWTH-21st Project<sup>42</sup>**

Turin has a population of approximately 910,500 inhabitants, and is a major industrial centre, known primarily for the aerospace and car manufacturing industries. Turin is a high-income city, with a GDP of US\$58 billion. Of the urban inhabitants, 13% are educated to university level. The four main obstetric departments deliver approximately 12,500 babies per year, including Azienda Ospedaliera OIRM—S. Anna (70%), Ospedale Maria Vittoria (13%), Ospedale Mauriziano Umberto I (9%), and Presidio Ospedaliero Martini (8%). Of these, Azienda

Ospedaliera OIRM—S. Anna was selected to take part in the longitudinal INTERGROWTH-21<sup>st</sup> Project, as it covered the largest number of births per year. Azienda Ospedaliera OIRM—S. Anna has a LBW prevalence of <10% and a mean BW of 3108g (Table 3.1). The site-specific socio-economic cut-off was defined as completion of middle-school (14 years of age).

### **3.3.1.2 Brazil**

The Brazilian city of Pelotas was selected as the Latin American site for the INTERGROWTH-21<sup>st</sup> Project. This is the same population from which the Pelotas 2004 birth cohort was drawn (although the INTERGROWTH-21<sup>st</sup> project were born 8-10 years later). Pelotas is in the southernmost region of the country, in the state of Rio Grande do Sul (Figure 3.1). Pelotas has approximately 340,000 inhabitants, the majority of which (92%) reside in urban areas. Pelotas can be classified as a middle-income city, with a gross domestic product (GDP) per capita of R\$16448 (US\$7399) in 2010<sup>43</sup>. The main economic activities in Pelotas are agriculture (predominantly rice and cattle) and services (including two universities). Furthermore, 47% of women in Pelotas receive >9 years of formal education<sup>43</sup>. There are approximately 4000 live births per year in Pelotas, more than 99% of which take place in the city's four maternity hospitals, Hospital Miguel Piltcher (5%), Hospital São Francisco de Paula (46%), Hospital Escola UFPEL (18%) and Santa Casa do Misericórdia (30%). The 2004 Pelotas birth cohort study indicated that the prevalence of LBW and IUGR are 10% and 12% respectively, and the mean BW is 3150g (Table 3.1). The site-specific socio-economic cut-off for Pelotas was a monthly family income greater than 3 times that of minimum wage.

### **3.3.1.3 India**

Nagpur, in the Indian state of Maharashtra was selected as the South Asian site for the INTERGROWTH-21<sup>st</sup> Project. Maharashtra is situated in the west-central region of India, with the city of Nagpur located inland (Figure 3.8).



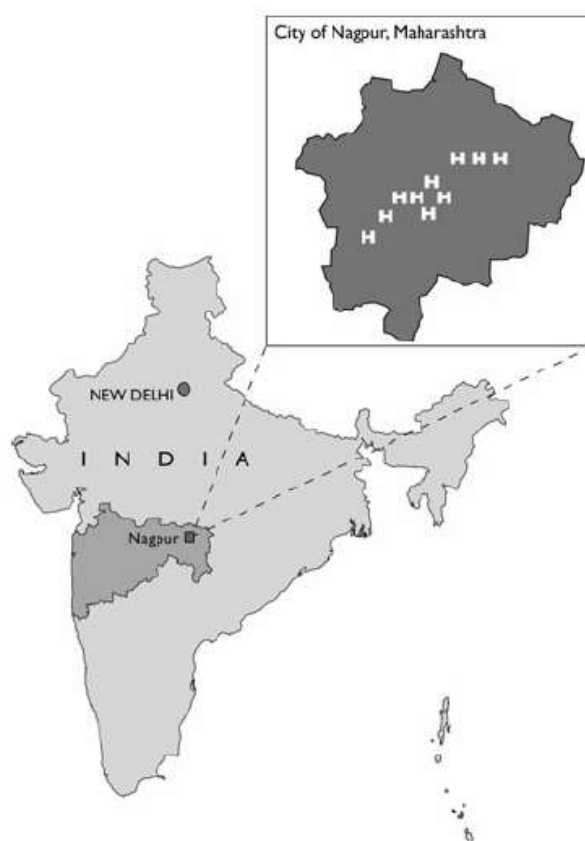


**Figure 3.8. Location of Nagpur, India. H = hospital participating in the INTERGROWTH-21st Project<sup>44</sup>**

Nagpur has an urban population of approximately 2,129,500, and is the largest central-Indian city. Nagpur can be classified as a middle-income city, with a monthly GDP per capita of INR11,666 (US\$208) in 2010-2011<sup>45</sup>. Nagpur is an important trading location in the Vidarbha region, and is a main centre of education and politics. There are approximately 4500 births per year in Nagpur, among the target population, 76% of which occur in ten hospitals including Ketkar Hospital (15%), Avanti Hospital (9%), Mulik Hospital & Research Center (9%), Renuka Nursing Home (9%), Om Women's Hospital (9%), Somani Nursing Home (8%), Saboo Nursing Home (7%), Avantika Hospital (5%), Nandlok Hospital (3%), and Gurukrupa Maternity Home (2%). Ketkar Hospital was selected as the focal point for the INTERGROWTH-21<sup>st</sup> study, and the majority of enrolled participants were from this hospital. The prevalence of LBW reported by Ketkar Hospital is 7.6%, with a mean BW of 3109g (Table 3.1). The site-specific socio-economic

cut-off for Nagpur was women with  $\geq 15$  years of schooling with a total family monthly income in excess of INR25,000.

### 3.3.1.4 Kenya

The Parklands suburb of Nairobi, the capital city of Kenya, was selected as the African site for the INTERGROWTH-21<sup>st</sup> Project (Figure 3.9). Despite a growing economy, Kenya still has a high prevalence of nutritional deficiency and disease (such as malaria and HIV). Furthermore, there is limited access to maternity services (with only 44% of births occurring in the presence of trained attendant), and a high maternal mortality (488 per 100,000 live births). Given this, care had to be taken in selecting a low-risk population for participation in the study. Parklands is a wealthy suburb in the city of Nairobi, and is a non-malaria endemic area.

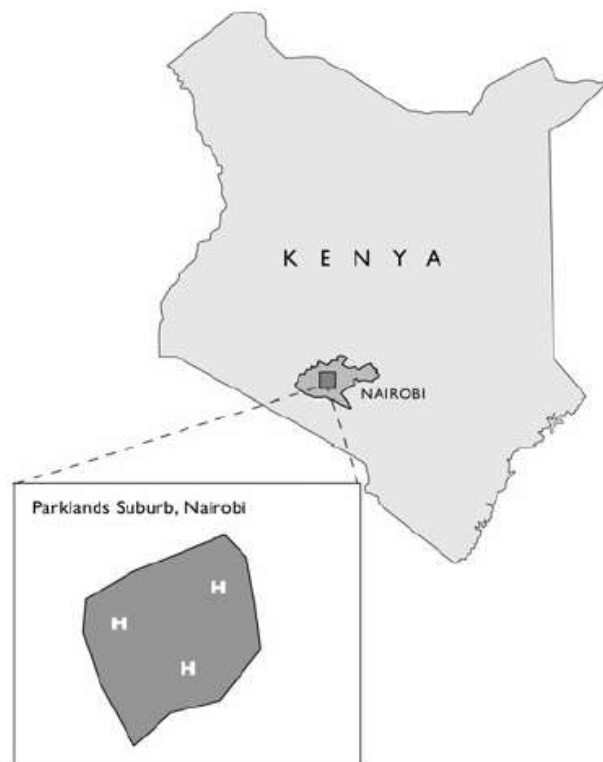


**Figure 3.9. Location of the Parklands suburb in Nairobi, Kenya. H = hospital participating in the INTERGROWTH-21st Project<sup>46</sup>**

Nairobi has a population of approximately 3.5 million, and a GPD of US\$12 billion. The population of Parklands is approximately 40,000, and the majority of Parklands inhabitants are affluent Kenyan families<sup>46</sup>. The neighbourhood is a mixture of commercial and residential properties, and is located approximately 5km from the Nairobi central business district. There are 3 obstetric units in the Parklands suburb with a total of approximately 4,200 annual deliveries: Aga Khan University Hospital (68%), Avenue Hospital (18%) and M.P. Shah Hospital (14%). All three participated in the INTERGROWTH-21<sup>st</sup> study, with the coordinating centre located at Aga Khan University Hospital. The prevalence of LBW is 11%, with a mean BW of 3101g (Table 3.1). The site-specific socio-economic cut-off was defined as ability to gain access to medical care without any financial barriers.

**Table 3.1. INTERGROWTH-21st protocol requirements**

| Indicator of low risk                       | Oxford,<br>Kingdom | United<br>Turin, Italy | Pelotas, Brazil | Nagpur, India | Parklands,<br>Kenya | Nairobi, |
|---------------------------------------------|--------------------|------------------------|-----------------|---------------|---------------------|----------|
| Low birth weight prevalence (%)             | 6                  | <10                    | 10              | 7.6           | 11                  |          |
| Perinatal mortality prevalence <sup>a</sup> | 0.8                | 4.8                    | 18.5            | 9.5           | 16.9                |          |
| Mean birth weight (g)                       | 3334               | 3108                   | 3150            | 3190          | 3101                |          |
| >4 years maternal education (%)             | >99                | >99                    | 92              | >80           | >80                 |          |
| Altitude (m above sea level)                | 55                 | 239                    | <500            | 310           | 1680                |          |

<sup>a</sup> per 1000 live births

### 3.3.2 Primary measures

#### 3.3.2.1 Obstetric measures

##### 3.3.2.1.1 Determination of gestational age

GA was determined using a two-stage combination of last menstrual period (LMP) and early ultrasound. First, women were asked to recall the date of their LMP for an estimation of GA. If the estimated GA was between 9<sup>+0</sup> and 13<sup>+6</sup> weeks, the date was then confirmed with a standardised crown-rump length (CRL) measurement, using an internationally recognised chart<sup>47</sup>. If the CRL estimation was within 7 days of the LMP estimate, then LMP was considered valid, and taken as true biological date. If there was more than 7 days discrepancy between estimates, the women were excluded from the study due to unreliable GA estimation. Furthermore, women were excluded from the study if the estimation fell outside the 9<sup>+0</sup> to 13<sup>+6</sup> week range.

##### 3.3.2.1.2 Birth anthropometric measurements

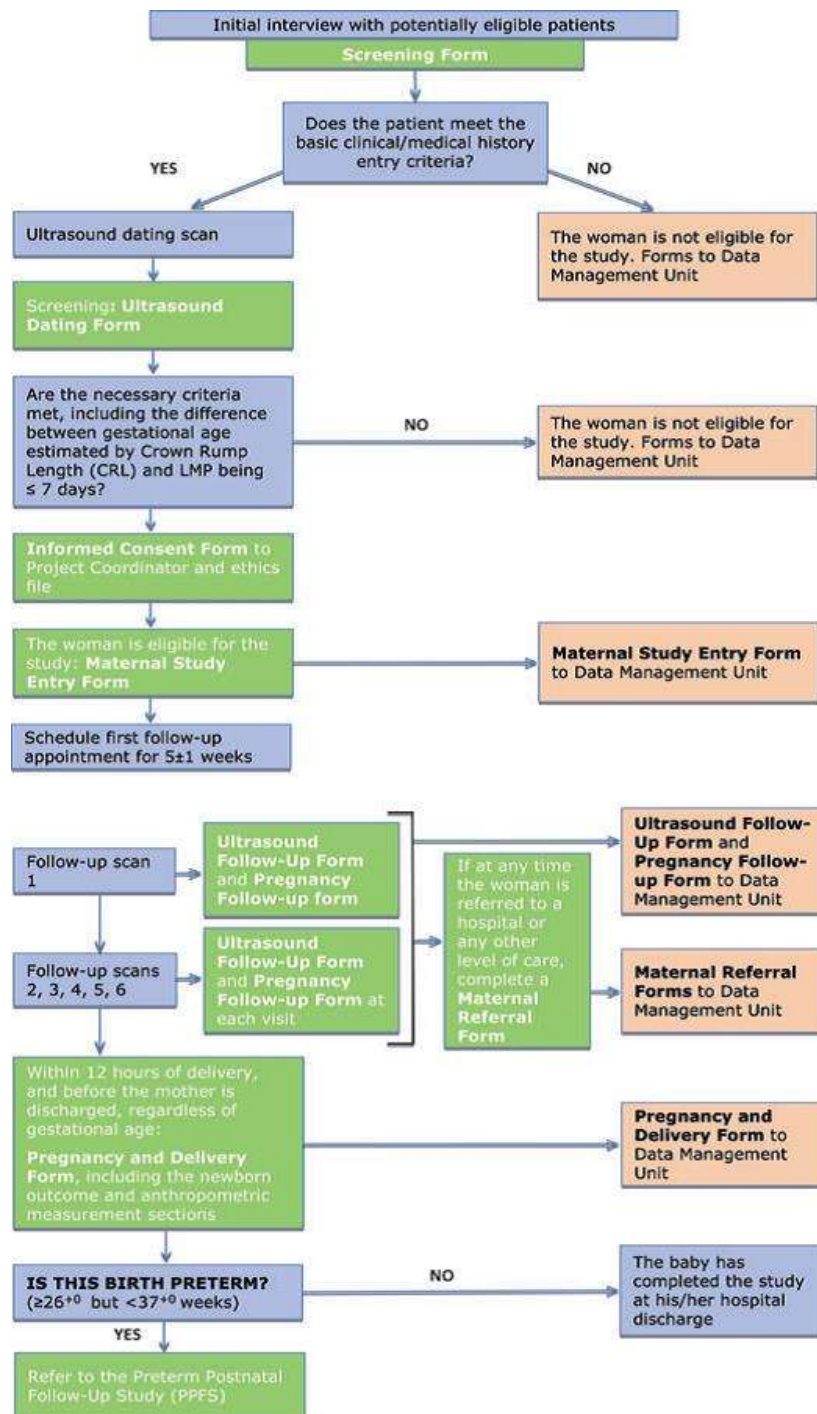
Neonatal measurements of BW, BL and HC were taken within 24 hours of birth. Infant weight was measured using a portable, electronic weighing scale (Seca model 376, Germany/China), with precision to 5g up to 7.5g, and 10g up to 20kg. BL was measured in the recumbent position using the Harpenden Infantometer (range 300-1100mm) (Chasmors Ltd., UK), which has a fixed headboard and moveable footboard with a digital counter to 0.1cm. HC was measured using a self-retracting, flat metal tape measure (CMS ref.3105, Chasmors Ltd, UK), 0.7cm wide, range 0-2m, precise to 1mm. To measure HC, the measuring tape is anchored just above the eyebrows at the front, and over the fullest protuberance of the skull at the back (Figure 3.10).



**Figure 3.10. Head circumference measurement at birth**

Measurement procedures were standardised based on the basis of WHO recommendations to ensure maximum validity<sup>48</sup>. Standardisation for the researchers collecting anthropometric measurements was conducted at each site prior to commencement of data collection and repeated every 3 months<sup>49</sup>. The initial standardisation at each site was carried out under the supervision of a visiting expert member of the INTERGROWTH-21<sup>st</sup> Anthropometry Group, and continued by the local lead anthropometrist at each site. The intraobserver and interobserver error of measurement values for BL ranged from 0.3-0.5 cm, and those for HC ranged from 0.3-0.4 cm. These standardisation sessions ensured anthropometrists were following the recommended techniques, monitored reliability (precision and accuracy), and enabled corrective action to be taken if required.

Each of the birth anthropometric measurements was taken once each by 2 independent anthropometrists. If a pair of measurements fell outside the maximum allowed difference (0.7cm for length, 0.5cm for HC and 50g for weight), the measurements were repeated. The percentage of times that measurements were taken by a single anthropometrist was 2.4% for BW, 0.1% for BL, and 1.0% for HC. In these cases the single measurement was used for analysis<sup>50</sup>. The flowchart for pre- and antenatal assessments is presented in Figure 3.11.

Figure 3.11. Patient flowchart for INTERGROWTH-21st<sup>3</sup>

### 3.3.2.2 Follow-up assessments

#### 3.3.2.2.1 The INTERGROWTH-21<sup>st</sup> Neurodevelopmental Assessment (INTER-NDA)

Infant neurodevelopment was assessed at 24 months of age, using the INTERGROWTH-21<sup>st</sup> Neurodevelopmental Assessment (INTER-NDA). The INTER-NDA assesses infant cognition, language (expressive and receptive), motor development (fine and gross) and behaviour (attention and social emotional development). The INTER-NDA was developed by an expert advisory panel, the INTERGROWTH-21<sup>st</sup> Infant Development Group, specifically for the purposes of the INTERGROWTH-21<sup>st</sup> study. It was designed to address the need for an assessment tool that could be used internationally across culturally diverse settings, could be rapidly administered, required few resources and no pre-existing infrastructure, and could be conducted by non-specialised research staff<sup>51</sup>. In contrast to the WPPSI-R, the INTER-NDA is designed to minimise examiner errors in scoring and administration, by using a direct, tablet-based application for scoring.

The INTER-NDA consists of 53 items selected from the Bayley Scales of Infant Development (BSID)<sup>52</sup>, the Rapid Neurodevelopmental Assessment (RNDA)<sup>53</sup>, Malawi Development Assessment Tool<sup>54</sup> the Griffiths Scales<sup>55</sup> and the CBCL 1.5-5<sup>56</sup> (Appendix X). The process for developing the INTER-NDA is presented in Figure 3.12. Previously, the inter-rater reliability (variability between different assessors on same subject) and intra-rater reliability (variability within a single assessor on a single subject) of the INTER-NDA was determined across 21 assessors in Brazil, India, Italy, Kenya and the UK using Cohen's kappas. These were found to be  $k = 0.70$ , 95% CI: 0.47–0.88 (for inter-rater reliability) and  $k = 0.79$ , 95%CI: 0.48–0.96 (for intra-rater reliability)<sup>57</sup>. The items from the subsets of the CBCL 1.5-5, which has also been previously validated, with the attention scale demonstrating good test-retest reliability ( $r=0.78$ ), moderate-good inter-rater reliability ( $r=0.52$ ), and good internal consistency ( $\alpha=0.85$ )<sup>56</sup>. As the INTER-NDA is a newly developed assessment tool, it has yet to be validated against a well-



established assessment for infant neurodevelopment. As such, Chapter 4 addresses this gap, and provides a validation of the INTER-NDA against a well-established, standardised assessment for infant neurodevelopment, the Bayley Scales of Infant Development, 3<sup>rd</sup> edition (BSID-III)<sup>58</sup>, and also assesses the internal consistency. The BSID-III was selected as the measure with which to validate the INTER-NDA as it is the current gold standard assessment for infant neurodevelopment. The BSID at 2 years of age has been shown to have significant predictive validity for the WPPSI-R at 4 years ( $r=0.41-0.45$ ,  $p<.001$ )<sup>59</sup>.

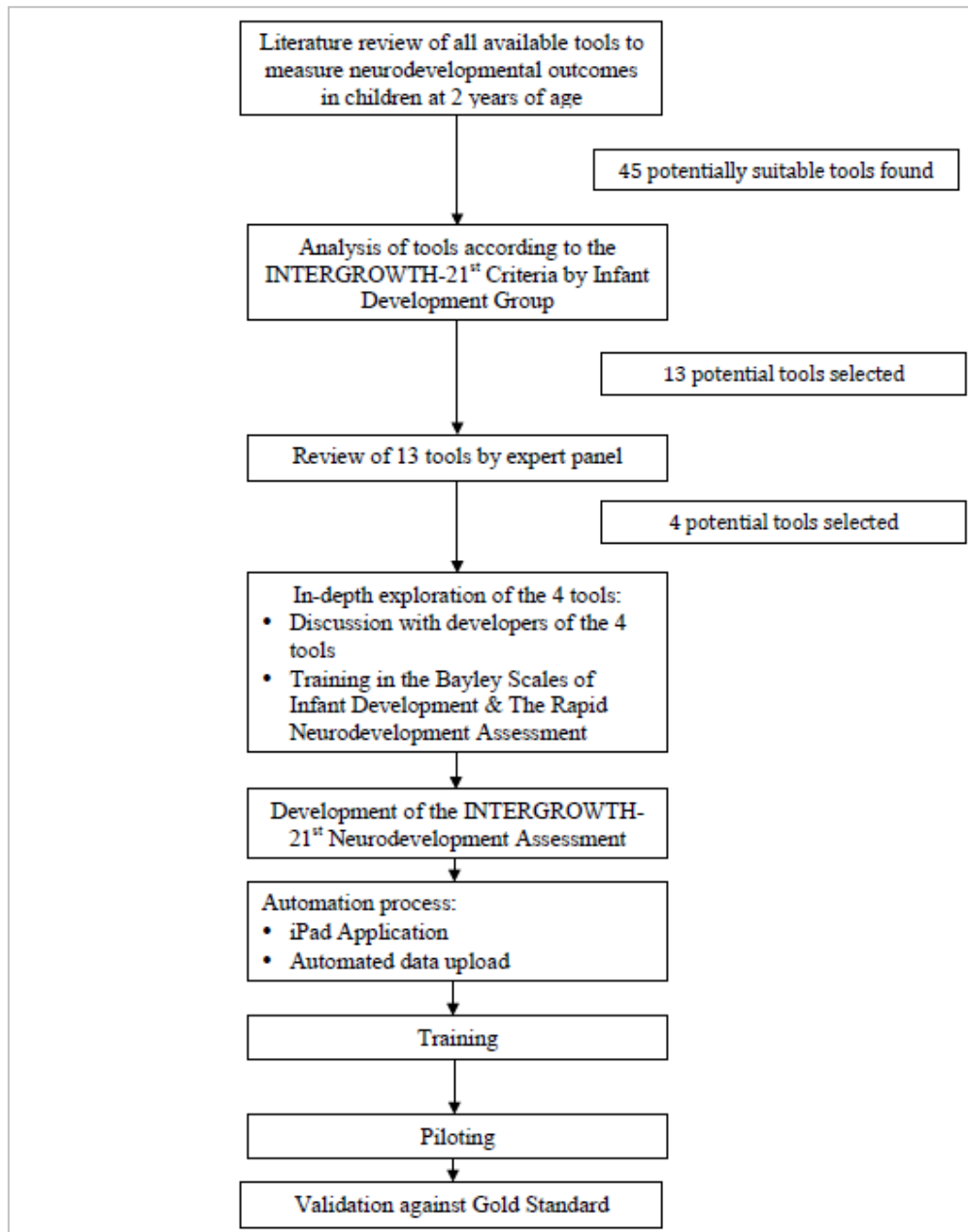


**Figure 3.12. Methodology for selection, design and development of the INTER-NDA<sup>57</sup>**

The INTER-NDA was conducted by trained researchers at each of the INTERGROWTH-21<sup>st</sup> sites, and scores were entered directly into a tablet-based application, the Neuroapp, developed specifically for use in the INTER-NDA (Figure 3.13; Figure 3.14). Data from the assessments was automatically transmitted to a centrally-managed database.



Figure 3.13. Screenshots from the cover page, data entry page and the neurodevelopment home page of the Neuroapp<sup>57</sup>

**Neurodevelopment Assessment Form: Part I** 0/00

**Neurodevelopment Assessment Form**

1. Builds a tower of 8 cubes in  $\leq 3$  trials (after demonstration, trials = 3). *(view picture)*

5 cubes    3-4 cubes    2 cubes    No attempt    Unable to assess

2. Names 4 colours when asked to do so. (Trials = 1) *(view examples)*

Names 4 colours    Names 3 colours    Names 1 or 2 colours

Does not name any colour    Unable to assess

3. Matches 3 cubes of same colours when asked (after demonstration, trials = 1). *(view picture)*

Matches 3 colours    Matches 2 colours    Matches 1 colour

Does not match any colour    Unable to assess

4. Hands examiner one cube when asked. (Trials = 1) *(view details)*

Hands only one block within 5 seconds

Hands only one block in more than 5 seconds

Hands two or more blocks

Does not hand any block / No attempt

Unable to assess

**NDA not performed** **HOME** **NEXT**

Figure 3.14. Screenshot of the INTER-NDA data entry section of the Neuroapp<sup>57</sup>

As part of the INTER-NDA, two subsets of the CBCL, the Attention and Emotional-Reactive subscales were completed by the mother during the assessment. The English version of the assessment form is presented in Appendix XI. This was translated into the local language for administration at the other INTERGROWTH-21<sup>st</sup> sites. Further information and psychometric properties of the CBCL are presented in section 3.1.2.2.1. The training materials and operation manual for the INTER-NDA are freely available at [www.intergrowth21.org.uk/protocol.aspx?lang51](http://www.intergrowth21.org.uk/protocol.aspx?lang51).

### 3.3.3 Confounding variables

Collection of data for confounding variables was conducted upon enrolment to the study (Appendix XII). Demographic data was self-report, and included maternal age, maternal education level, marital status, occupational status and paternal age. Obstetric data included number of previous pregnancies, number of previous births, and the first day of the LMP. Data collected regarding the current pregnancy included maternal weight and height. Maternal weight was measured using a Seca 877 Scale (Seca, Germany), accurate to the nearest 100g, with footmarks pasted to ensure standing position was uniform between measurements. Maternal height was measured using the Seca Stadiometer 242 (Seca, Germany), with a range of 62 to 210cm, and accuracy to 0.2cm. Maternal BMI at enrolment was calculated as  $BMI = \frac{[weight\ (kg)]}{[height\ (m)]^2}$ . At the perinatal interview (conducted within 24 hours postnatally), further information was collected on smoking, alcohol and recreational drug-use during pregnancy, maternal health during pregnancy, mode of delivery (caesarean section or vaginal birth), GA at birth, APGAR score at 5 minutes, infant sex, admission to the neonatal intensive care unit (NICU), and number of days in the NICU (Appendix XIII). Mothers who reported smoking, alcohol, recreational drug-use or mental illness during pregnancy were excluded.

A comparison of the Pelotas, ALSPAC and INTERGROWTH-21st cohorts on sample characteristics and anthropometric assessment and follow-up methodologies are presented in Table 3.2 and Table 3.3.

**Table 3.2. Comparison of the Pelotas, ALSPAC and INTERGROWTH-21st cohorts on sample characteristics and anthropometric measurement methodologies**

|                               | Pelotas 2004       | ALSPAC             | INTERGROWTH-21st                        |                         |                         |                         |                         |                         |
|-------------------------------|--------------------|--------------------|-----------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
|                               | Full cohort        | Full cohort        | Full cohort                             | Oxford (UK)             | Turin (Italy)           | Pelotas (Brazil)        | Nagpur (India)          | Nairobi (Kenya)         |
| <b>Sample characteristics</b> |                    |                    |                                         |                         |                         |                         |                         |                         |
| Location                      | Pelotas (Brazil)   | Avon (UK)          | Oxford, Turin, Pelotas, Nagpur, Nairobi | Oxford (UK)             | Turin (Italy)           | Pelotas (Brazil)        | Nagpur (India)          | Nairobi (Kenya)         |
| Years of recruitment          | 2004               | 1991-1992          | 2012-2014                               | 2012-2014               | 2012-2014               | 2012-2014               | 2012-2014               | 2012-2014               |
| Total <i>N</i> recruited      | 4231               | 14 541             | 2803 <sup>1</sup>                       | 640                     | 509                     | 411                     | 625                     | 617                     |
| <i>N</i> retained in sample   | 3749               | 7829               | 1066                                    | 168                     | 206                     | 108                     | 252                     | 319                     |
| Loss-to-follow-up (%)         | 11.4%              | 53.8%              | 61.6%                                   | 73.7%                   | 59.5%                   | 73.7%                   | 59.7%                   | 48.8%                   |
| Sample composition            | Mixed-risk         | Mixed-risk         | Low-risk                                | Low-risk                | Low-risk                | Low-risk                | Low-risk                | Low-risk                |
| World Bank economic status    | Upper-middle       | High-income        | Mixed                                   | High-income             | High-income             | Upper-middle            | Lower-middle            | Low-income              |
| <b>Measurement methods</b>    |                    |                    |                                         |                         |                         |                         |                         |                         |
| Birth weight                  | Maternity staff    | Birth records      | Two trained researchers                 | Two trained researchers | Two trained researchers | Two trained researchers | Two trained researchers | Two trained researchers |
| Birth length                  | Trained researcher | Trained researcher | Two trained researchers                 | Two trained researchers | Two trained researchers | Two trained researchers | Two trained researchers | Two trained researchers |
| Head circumference            | Trained researcher | Trained researcher | Two trained researchers                 | Two trained researchers | Two trained researchers | Two trained researchers | Two trained researchers | Two trained researchers |

<sup>1</sup> *N* includes *births* in the five neurodevelopment sites only

**Table 3.3. Comparison of the Pelotas, ALSPAC and INTERGROWTH-21st follow-up assessment methodologies**

|                                | Pelotas 2004            | ALSPAC               | INTERGROWTH-21st         |
|--------------------------------|-------------------------|----------------------|--------------------------|
| <b>Attention assessment</b>    |                         |                      |                          |
| Assessment tool                | CBCL 4-18 <sup>10</sup> | SDQ <sup>28</sup>    | CBCL 1.5-5 <sup>56</sup> |
| Age at assessment              | 4 years                 | 6 years              | 2 years                  |
| Tool age range                 | 4-18 years              | 3-16 years           | 18 months-5 years        |
| Number of items (total)        | 113                     | 25                   | 16                       |
| Number of subscales            | 8                       | 5                    | 2                        |
| Scoring format                 | Likert (3 point)        | Likert (3 point)     | Likert (3 point)         |
| Duration of assessment (total) | 20 mins                 | 10 mins              | 5 mins                   |
| Test-retest reliability        | $r=0.92^{13}$           | $r=0.71^{30}$        | $r=0.78^{56}$            |
| Inter-rater reliability        | $r=0.78^{13}$           | $r=0.47^{30}$        | $r=0.52^{56}$            |
| Internal consistency           | $\alpha=0.73^{13}$      | $\alpha=0.75^{30}$   | $\alpha=0.85^{56}$       |
| <b>Cognitive assessment</b>    |                         |                      |                          |
| Assessment tool                | WPPSI-R                 | WPPSI-R              | INTER-NDA                |
| Age at assessment              | 4 years                 | 4 years              | 2 years                  |
| Tool age range                 | 30 months-7.25 years    | 30 months-7.25 years | 22-28 months             |
| Number of items (total)        | 293 <sup>i</sup>        | 293 <sup>i</sup>     | 53                       |
| Number of subscales            | 14                      | 14                   | 6                        |
| Scoring format                 | Binary (pass/fail)      | Binary (pass/fail)   | Likert (5 point)         |
| Duration of assessment         | 90 mins                 | 90 mins              | 15-20 mins               |
| Test-retest reliability        | $r=0.90^{15}$           | $r=0.90^{15}$        | -                        |
| Inter-rater reliability        | $r=0.82^{16}$           | $r=0.82^{16}$        | $k=0.70^{57}$            |
| Internal consistency           | $\alpha=0.97^{17}$      | $\alpha=0.97^{17}$   | $\alpha=0.67-0.90^{57}$  |

CBCL=Child Behaviour Checklist; SDQ=Strengths and Difficulties Questionnaire; WPPSI-R=Weschler Preschool and Primary Scale of Intelligence-Revised; INTER-NDA=INTERGROWTH-21<sup>st</sup> Neurodevelopmental Assessment; <sup>i</sup> Maximum score, most children will not complete all items.

### 3.4 Calculation of birth anthropometric indices across all three cohorts

Identical methods of classifying neonates based on anthropometric indices were used for all three cohorts. Four broad groups of anthropometric indices were included – BW indices (including crude BW and weight-for-age indices), stunting indices (including HC and BL), wasting indices (including ponderal index (PI) and body mass index (BMI)) and asymmetry indices (including HC/BL, HC/PI and HC/BMI).

For BW indices, neonates were classified as LBW if their BW fell under 2500g, in accordance with the definition of LBW by the World Health Organisation (WHO)<sup>60</sup>. SGA was classified using one reference and two standards, the reference using a pre-existing, widely used chart for birth weight-for-gestational-age-and-sex (Table S3.1)<sup>61</sup> and the standards using the Multicentre Growth Reference Study (MGRS) standard (Table S3.2)<sup>62</sup> and the INTERGROWTH-21<sup>st</sup> standard (Table S3.3)<sup>63</sup>. Neonates were classified as SGA if their birth BW-for-GA fell below the 10<sup>th</sup> percentile, the most commonly used cut-off for defining SGA births<sup>64</sup>. Area under the curve (AUC) analysis showed that the MGRS standards had the highest AUC (meaning that more neonates would be classified as having impaired growth using this standard compared to the others; Figure S3.1).

Measures of HC and BL were used as indicators of stunting. BL and HC were considered stunted if they fell below the 10<sup>th</sup> percentile against either of 2 standards, the MGRS standards (Table S3.2)<sup>62</sup> and the INTERGROWTH-21<sup>st</sup> Project standards (Table S3.3)<sup>63</sup>. AUC analysis showed that the MGRS standards had higher AUC than INTERGROWTH-21<sup>st</sup> for both BL (Figure S3.2) and HC (Figure S3.3), meaning that more children would be classified as growth impaired according to MGRS standards than by INTERGROWTH-21<sup>st</sup> standards.

Wasting indices included were PI and BMI. PI was calculated according to Rohrer's formula, and BMI calculated according to the formulas below:



$$PI = \frac{birthweight(kg)}{birthlength(m)^3}$$

$$BMI = \frac{birthweight(kg)}{birthlength(m)^2}$$

Both PI and BMI were included as indicators of wasting, as there is disagreement about which is the most effective for identifying neonatal wasting<sup>65</sup>. For comparability to the stunting indices, neonates were considered wasted if their PI or BMI fell below the 10<sup>th</sup> percentile against either of two references (the bottom 10<sup>th</sup> percentile of the sample, or the bottom 10<sup>th</sup> percentile of the sample-for-GA).

Asymmetry indices were used to quantify the ratio of HC to other anthropometric indices, as an indicator of fetal circulatory redistribution (FCR). Asymmetry indices included HC/BL, HC/PI and HC/BMI. Growth was considered asymmetric if the ratios were above the 90<sup>th</sup> percentile for each cohort (representing a proportionally larger HC compared to other indices (BL, PI or BMI)).

### **3.5 Statistical power estimation**

A statistical power analysis was performed to ascertain the suitability of each cohort, based on sample size, to detect effects of various magnitudes (Figure 3.15). The range of ORs included in the analysis was based on the effect size identified in the systematic review (Chapter 2) and the range of ORs reported in previous studies. The analysis was based on an alpha=.05 and power=.80, and was conducted for logistic regression analyses using G\*Power 3<sup>66</sup>. Figure 3.15 shows that all three cohorts will have the power to detect small but significant effects (OR>1.20) for unadjusted associations. For adjusted associations however, larger samples will be required to detect significant associations.

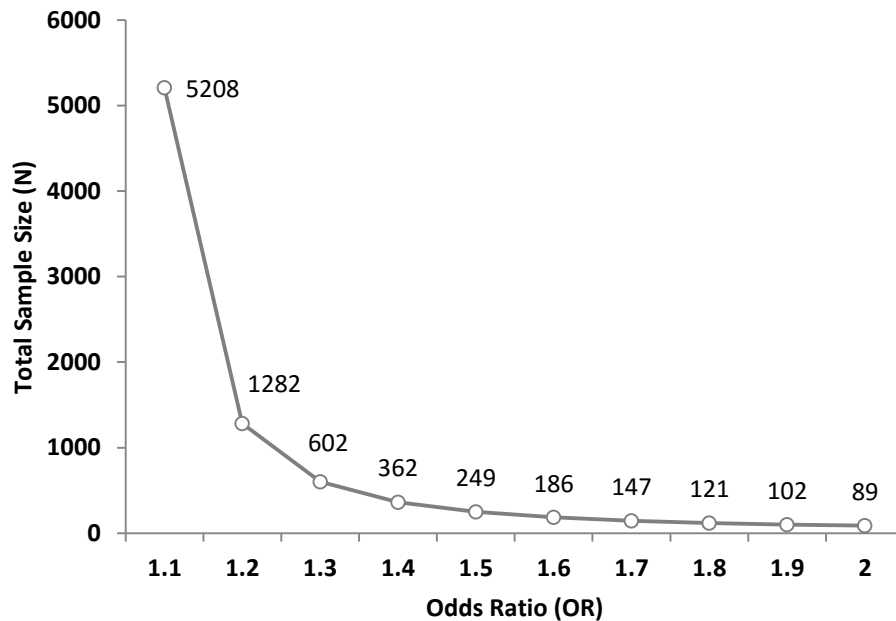


**Figure 3.15. Statistical analysis of power of each cohort to detect effects of various magnitudes ( $\alpha = .05$ , power  $[1-\beta] = .80$ )**

## 3.6 General statistical approach and considerations

### 3.6.1 Data screening

Data was screened for the presence of erroneous values (for example neurodevelopmental scores above the maximum). Erroneous values were removed ( $n=2$ ). Data was also screened for the presence of outliers. As the cohorts are descriptive in nature and to avoid skewing the representativeness of the data, outliers were retained in the analyses so long as values were not erroneous, as described above. The distribution of attention and cognitive data was examined for normality to determine whether parametric or non-parametric tests would be most appropriate. Histograms of distribution of attention and cognitive scores are presented in supplementary Figure S3.4. As is usual with data obtained from parent-report

attention questionnaires, the attention data was non-normally distributed, with strong positive skew (larger number of children scoring low values than scoring high values). As such, statistical analyses relying on assumption of normality (i.e. univariate ANOVAs) were replaced with Kruskal-Wallis nonparametric tests for attention outcomes, which do not rely on the assumption of normality.

### **3.6.2 Statistical analysis approach**

There are a number of different statistical approaches that have been used in research examining the effect of impaired fetal growth on long-term outcomes. Generally, the selection of statistical technique should be based on consideration of the type of data to be analysed, and the research questions to be addressed<sup>67</sup>. The general statistical approach taken to answer the research questions (Chapters 5-7) was therefore a multistage approach, drawing on a number of statistical methods from psychology, epidemiology and public health research.

1. **Difference in mean scores:** To assess whether there is an observable difference in mean scores, and to justify further analysis, Kruskal-Wallis tests for attention outcomes and univariate ANOVAs for cognitive outcomes are used to examine group differences in attention and cognitive scores.
2. **Logistic regression analyses:** Logistic regression was conducted with hierarchical adjustment for confounding variables. This adjustment method is common in epidemiological studies of childhood impairments/illness<sup>68</sup>, and allows each level of confounders to be successively built in to the model based on the timing of the factors affecting development. This allowed a comparison between the different models, to identify which group of confounding variables may have had the biggest effect on the association between birth anthropometric indices and neurodevelopmental outcomes. Confounders were selected based on a statistical threshold of association with the exposure (birth anthropometric indices) and outcome (attention or cognitive

development), as well as those variables that have been previously identified as confounders of this relationship (theoretical basis). This is a conservative approach to analysis, however is appropriate for large observational studies and datasets. Even using this conservative approach to confounder adjustment, it is possible that there may be residual confounding from unobservable confounding factors<sup>69</sup>. These regression analyses constituted the primary analyses of the data, and were thus conducted on both continuous outcomes scores (presented in the main text) and binary outcome scores (presented in the appendices). Consistency between patterns of association using both continuous and binary data indicates more robust findings.

3. **Sensitivity, specificity and receiver operating characteristic analysis:** Sensitivity and specificity and receiver operating characteristics (ROC) analysis was conducted. Sensitivity and specificity analysis allow identification of how well the birth anthropometric indices separate those who will develop neurodevelopmental impairments from those who will not. Sensitivity measures the proportion of those with fetal growth impairment, identified at birth, with poor neurodevelopmental outcomes. Sensitivity changes with different cut-off points (i.e. a higher cut-off point will yield higher sensitivity). The formula for calculating sensitivity is:

$$\text{Sensitivity} = \frac{\text{number of true positives}}{\text{number of true positives} + \text{number of false negatives}}$$

Specificity measures the proportion of those with normal fetal growth, measured at birth, whose neurodevelopmental outcomes will be in the normal range. Specificity also changes with cut-off point, and is inversely related to sensitivity (i.e. a lower cut-off point will yield higher specificity). The formula for calculating specificity is:

$$\text{Specificity} = \frac{\text{number of true negatives}}{\text{number of true negatives} + \text{number of false positives}}$$

Variability in sensitivity and specificity across populations is expected for outcomes such as neurodevelopment, which may be influenced by several factors<sup>70</sup>. Sensitivity and specificity values allow for the calculation of positive and negative predictive values<sup>71</sup> (i.e. how likely it is that a child with impaired fetal growth will/will not have attention or cognitive impairments). ROC analyses allow quantification of the predictive value of an indicator. The area under the curve (AUC) provides an index of accuracy, assessing the possibility of correctly identifying a randomly selected pair of cases in which one is growth restricted and one is not.

### **3.6.3 Multiple comparison consideration**

The analysis in the current thesis used multiple anthropometric measurements, thus requiring multiple statistical tests across three cohorts. Multiple comparisons inflate the likelihood of Type I error, and can lead to erroneous conclusions<sup>72</sup>. It was a priori decided, however, to not apply a mathematical correction to the alpha value of the regression analyses (e.g. Bonferroni correction), for two reasons. Firstly, as the number of Type I errors cannot decrease without a corresponding increase in the number of Type II errors, applying a statistical adjustment, particularly when more than five comparisons are being made (as was the case in the current study) can lead to an unacceptable over-inflation of the Type II error rate<sup>73</sup>. A high rate of Type II errors can mean that associations that are present are being missed, and given that anthropometric measurements were being tested as indicators of potential risk for neurodevelopmental delay, a high Type II error rate is not appropriate within this theoretical framework. Secondly, the theoretical assumption behind the correction for multiple comparisons is that all null hypotheses are true simultaneously (universal null hypothesis)<sup>74</sup>, which was not relevant to the current study. Instead of using adjustments for multiple

comparisons in such cases, clear description, theoretical justification for analytic methods, and presentation of full probability values ( $p$  values) are suggested as acceptable methods of adequately addressing multiple comparisons<sup>75</sup>. The current thesis has addressed each of these recommendations in statistical analysis and results reporting.

All analyses were performed using IBM SPSS Statistics for Windows 21.0<sup>76</sup> Specific statistical methodology is discussed further in each chapter.

### **3.7 Rationale for the scope of research design and methodology**

As with all longitudinal, prospective birth cohort studies, there was a large amount of data available for analysis. As such, a number of *a priori* decisions were made regarding the design and methodology, to ensure: 1) ability to clearly address the research questions; 2) clear identification and definition of variables of interest; and 3) comparability between cohorts.

Birth anthropometric indices were limited to those that were available for all three cohorts. Tenth percentile cut-off points were chosen for consistency with previous research and global recommendations on birth anthropometric indices provided by the WHO<sup>67</sup>, and also to isolate those cases that are growth restricted whilst maintaining adequate power to identify associations. The inverse (90<sup>th</sup> percentile cut-off point) was used for the asymmetry indices, to represent a proportionally larger HC in comparison to other anthropometric indices). It must be noted, however, that this constitutes a statistical definition of fetal growth impairment indices at birth, and as such, will include some neonates that are normally grown but constitutionally small.

Two reference values for each of the stunting and wasting measures were included to more clearly distinguish the effects of small size at birth, compared to neonates with small size for GA at birth, and also to provide an alternative standard that may be useful in settings where reliable estimation of GA is not available (as is common in LICs)<sup>67</sup>. Two references for SGA were

included to compare the newly developed INTERGROWTH-21<sup>st</sup> SGA standard (derived from eight geographically diverse sites), with a pre-existing widely used reference (derived from a North American sample).

Two primary neurodevelopmental outcomes (attention and cognition) were selected for further examination following the systematic review (Chapter 2). These outcomes were selected because they were shown to have consistent associations with fetal growth impairment (as opposed to other neurodevelopmental domains for which the associations were more mixed). Objective assessments were available for cognition in all 3 cohorts, however only parental report measures were available for attention across all 3 cohorts. One reason for this is that direct measures of child attention (such as eye tracking or continuous performance tests) are often not feasible in large samples, as they are very resource-intensive, requiring technological infrastructure (hardware and software) for home visits, or lab-based assessment<sup>77,78</sup>.

Four attentional functions have been suggested in infancy and early childhood: alertness, spatial orienting, attention to object features and endogenous attention<sup>79</sup>. Endogenous attention is the last of these to develop, and refers to easily observable constructs of attention, including attention span, distractibility and persistence. Parent-report measures of attention, therefore, most closely relate to endogenous attention, and capture parental perception of the child's ability to self-regulate attentional processes<sup>80</sup>. Parent-report scales of attention impairments reflect external manifestations of attention problems, i.e. externalising symptoms<sup>81</sup>. As externalising symptoms are publically observable, regular adult observers (such as parents) are valuable informants<sup>82</sup>. Parent-report rating scales have been shown to be significantly associated with objective attention assessments in childhood, such as computerised continuous performance tests of attention<sup>83,84</sup>. Furthermore parental-report measures at 4 years of age have been shown to have significant predictive validity for clinical-level attention impairments at age 6<sup>84</sup>. For consistency and comparability, parental-report assessments of

attention were included for all 3 cohorts (CBCL and SDQ). These measures have been shown to have high overall concurrent validity, and particularly so for attention ratings ( $r=0.75$ )<sup>32</sup>. Comparability of outcome measure between cohorts was given primacy over identical age at follow-up (so long as the age at assessment was within a reasonable limit, maximum 4 years). For cognitive outcomes, objective assessments were used (WPPSI-R and INTER-NDA). The INTER-NDA was largely derived from items on the BSID, which has been shown to have good predictive validity for the WPPSI-R at 4 years ( $r=0.41-0.45$ ,  $p<.001$ )<sup>59</sup>. As the INTER-NDA had not previously been validated as a neurodevelopmental assessment tool, a validation study was conducted on the INTER-NDA for inclusion in the current thesis. All assessments have been shown to have good stability over time (CBCL  $r=0.58$ <sup>56</sup>; SDQ  $r=0.62$ <sup>31</sup>; WPPSI-R  $r=0.84$ <sup>85</sup>) and as such, age at assessment was given scope for limited variation.

The inclusion of data on potential confounding variables was based on those that have been identified as risk factors for impaired fetal growth, neurodevelopment or both, in previous research with the Pelotas and ALSPAC cohorts, and also more broadly in other research in the field. In the case of the INTERGROWTH-21<sup>st</sup> study, as mothers were selected as being optimally healthy, confounding variables were selected based on those that were identified as having associations in the Pelotas and ALSPAC cohorts, namely maternal education, maternal age at delivery, maternal BMI at enrolment, delivery mode and neonatal APGAR score at 5 minutes. A comparison of the Pelotas, ALSPAC and INTERGROWTH-21<sup>st</sup> cohorts on sample power and previous risk factors for attention and cognitive impairment within-cohorts is presented in Table 3.4.



**Table 3.4. Comparison of the Pelotas, ALSPAC and INTERGROWTH-21st cohorts on sample power and previous risk factors for attention and cognitive impairment within-cohorts**

|                                                                                       | Pelotas 2004                                                                                                                                                                | ALSPAC                                                                                                                                                                                                                   | INTERGROWTH-21st                                                                                 |
|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Power <sup>i</sup>                                                                    | 0.99-1.00                                                                                                                                                                   | 1.00                                                                                                                                                                                                                     | Full cohort = 0.87<br>UK = 0.24<br>Italy = 0.27<br>Brazil = 0.18<br>India = 0.31<br>Kenya = 0.37 |
| Factors previously identified as associated with attention in childhood <sup>ii</sup> | Maternal smoking; socioeconomic disadvantage; anxiety during pregnancy; depression during pregnancy; excessive crying in early infancy; genetic factors                     | Physical activity; depression during pregnancy; anxiety during pregnancy; genetic factors; child diet; maternal diet during pregnancy; postnatal mental health; parent-child relationship; paternal postnatal depression | No published research as yet                                                                     |
| Factors previously identified as associated with cognition in childhood <sup>ii</sup> | Maternal schooling, socio-economic position; child stimulation; APGAR<7; gestational diabetes; short inter-pregnancy interval; preterm delivery; history of hospitalisation | Maternal diet; maternal weight; resuscitation at birth; prenatal methylmercury exposure; maternal postnatal depression; prenatal alcohol exposure; maternal education level                                              | No published research as yet                                                                     |

<sup>i</sup> Estimate based on odds ratio (OR) range = 1.20-1.30; <sup>ii</sup> exposures identified to be associated with attention or cognition within each cohort

### **3.8 Summary**

Data from 3 longitudinal prospective birth cohort studies (the 2004 Pelotas Birth Cohort, the ALSPAC cohort, and the INTERGROWTH-21st Project cohort), have been included in this thesis to examine associations between indices of impaired fetal growth, measured at birth, and attention and cognitive development in childhood. Birth anthropometric indices were classified into 4 growth-indicator categories, including BW (<2500g and SGA), stunting (BL or HC), wasting (PI or BMI) and asymmetry (HC/BL, HC/PI or HC/BMI ratios). Attention was assessed using the CBCL or SDQ, and cognition was assessed using the WPPSI-R or INTER-NDA. The CBCL, SDQ and WPPSI-R are well-established measures of attention and cognitive development, with demonstrated validity. The INTER-NDA has not previously been validated, and as such, will be validated in the next chapter (Chapter 4).

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## **4 Validation of the INTERGROWTH-21<sup>st</sup> Neurodevelopmental Assessment (INTER-NDA) as an assessment of infant neurodevelopment**

### **Chapter outline**

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## 4.1 Introduction

The INTERGROWTH-21<sup>st</sup> Project used a custom-developed neurodevelopmental assessment, the INTERGROWTH-21<sup>st</sup> Neurodevelopmental Assessment (INTER-NDA) to assess neurodevelopment at 2 years of age. This assessment tool has yet to be validated against a current gold standard neurodevelopmental assessment. As such, a validation of the INTER-NDA against the current gold standard neurodevelopmental assessment, the Bayley Scale of Infant Development, 3<sup>rd</sup> edition (BSID-III)<sup>6</sup> was conducted, at 2 years of age. This validation study is presented in the current chapter.

Assessment at 2 years of age is important because this is the earliest point in early child development at which: (i) neurodevelopment is not confounded by transient neurological syndromes of prematurity<sup>1</sup> and (ii) conventionally used developmental instruments, such as the BSID, have been found to possess an acceptable level of medium- and long-term predictive validity<sup>2</sup>. Furthermore, the systematic review in Chapter 2 showed that neurodevelopmental impairment in some domains (such as cognition), cannot be readily assessed in infants with fetal growth impairment until 2 years of age.

A further rationale for assessment at 2 years of age is that the National Health Service (NHS) of the UK and Public Health England, recently formally prioritised 'health and wellbeing at 2 years' as a high-impact priority area<sup>3</sup>. This publication recommended the development of an indicator to assess child development at two years<sup>3</sup>. Currently, however, there is no validated screening tool which is quick and easy to administer, available to be used in general clinical practice to identify children who may require further neurodevelopmental assessment<sup>4</sup>.

### 4.1.1 The INTERGROWTH-21<sup>st</sup> Neurodevelopmental Assessment (INTER-NDA)

The INTER-NDA is designed to bridge the current gap in neurodevelopmental assessments, providing a tool that can assess infant neurodevelopment rapidly (15-20 minutes), without the need for specialised training or infrastructure, and is relatively free from cultural

biases (for materials used, see Figure 4.1). It assesses neurodevelopment across a number of domains, which can be combined into composite scores (Table 4.1). Details on the strategy leading to the development of the INTER-NDA are presented in Chapter 3 (section 3.3.2.2.1).



**Figure 4.1. Constituent items of the INTER-NDA assessment**

**Table 4.1. Scoring System of the INTER-NDA**

| Domain                      | Total Score                                | Mean score                             | Composite            | Composite score                                 |
|-----------------------------|--------------------------------------------|----------------------------------------|----------------------|-------------------------------------------------|
| <b>Cognition</b>            | $\Sigma$ (1,2,4,5,6,7,8,11,12,13,14,16,18) | Mean (1,2,4,5,6,7,8,11,12,13,14,16,18) | Cognition            | Mean cognitive score                            |
| <b>Expressive Language</b>  | $\Sigma$ (3,7,23,24,25, 26,27,28,29,30)    | Mean (3,7,23,24,25,26,27,28,29,30)     | Overall Language     | Mean of expressive and receptive language score |
| <b>Receptive Language</b>   | $\Sigma$ (5,8)                             | Mean (5,8)                             | Overall Language     |                                                 |
| <b>Fine Motor</b>           | $\Sigma$ (9,10,15,20)                      | Mean (9,10,15,20)                      | Overall Motor        | Mean of fine and gross motor score              |
| <b>Gross Motor</b>          | $\Sigma$ (19,21,22)                        | Mean (19,21,22)                        | Overall Motor        |                                                 |
| <b>Positive Behaviour</b>   | $\Sigma$ (31,32,33,34,35)                  | Mean (31,32,33,34,35)                  | Overall Behaviour    | Mean positive and negative behaviour score      |
| <b>Negative Behaviour</b>   | $\Sigma$ (36,37)                           | Mean (36,37)                           | Overall Behaviour    |                                                 |
| <b>Attention</b>            | $\Sigma$ (39,40,44,45,50)                  | Mean (39,40,44,45,50)                  | Attention            | Mean attention score                            |
| <b>Emotional reactivity</b> | $\Sigma$ (41,42,43,46,47,48,49,51,52)      | Mean (41,42,43,46,47,48,49,51,52)      | Emotional Reactivity | Mean emotional reactivity score                 |

The INTER-NDA is primarily based upon objective assessment of the child's performance<sup>2</sup>, with some additional items assessed by maternal-report (Table 4.2). Outcomes are reported on a 5-point scale (0=not assessable; 1=unable to complete; 2=some completion; 3=almost complete; 4=fully complete) characterising the child's performance in each domain along a spectrum. As such, the INTER-NDA may provide a more nuanced account of a child's ability compared to binary scoring systems (such as that used in the BSID-III) that mark a child as having simply 'passed' or 'failed' an item.

As an example of this key difference, a single child may be able to accumulate some points on the INTER-NDA for semi-completion, but this is not possible with the BSID-III. On item 1 of the INTER-NDA (which involves the child building a tower of 5 cubes), assessors score the total number of cubes in the child's tallest tower at the end of 3 trials (0-5). Similarly, on item 2

on the INTER-NDA (which involves naming 4 colours), assessors score the number of colours the child was able to name (0-4). For both these items on the BSID-III however, the child is scored only a 1 (pass) or 0 (fail). As such, for these two items, a child who is able to build *some* of a tower or name *some* colours would score an intermediate score on the INTER-NDA (3-6 out of a possible 8). A child who is not able to build a tower (<2 blocks) or name any colours (0 colours) would score a 2 (lowest score for administered items) on the INTER-NDA. Both of these children would score 0 on the BSID-III, highlighting the ability of the Likert-style scoring system of the INTER-NDA to provide a more nuanced differentiation of a child's developmental abilities.

The commonly reported administrative and technical errors in psychometric tests such as the BSID have been reported to be due to mistakes in the calculation of corrected age and scoring, errors in table referral and data entry errors<sup>5</sup>. It is estimated that these errors occur in approximately 38.5% of assessments, accounting for inaccuracies in more than 10% of reported composite scores<sup>5</sup>. In order to address this, the child's performance on the INTER-NDA is scored on a tablet-based application with integrated operational cues and quality checks<sup>2</sup>. Dimension and total scores are calculated by the application, and data is uploaded to the server in real time, ensuring no data entry errors. In order to minimise errors in the administration of the tests, all assessors are assessed at 3-monthly intervals by an 'expert assessor', using a protocol adherence checklist.

**Table 4.2. INTER-NDA subscales and methods of administration**

| Domain               | Directly administered | Maternal report | Concurrently scored <sup>1</sup> | Total items |
|----------------------|-----------------------|-----------------|----------------------------------|-------------|
| Cognition            | 12                    | 1               | -                                | 13          |
| Language             | 5                     | -               | 5                                | 10          |
| Fine Motor           | 4                     | -               | -                                | 4           |
| Gross Motor          | -                     | 3               | -                                | 3           |
| Behaviour            | -                     | -               | 7                                | 7           |
| Attention            | -                     | 5               | -                                | 5           |
| Emotional reactivity | -                     | 11              | -                                | 11          |
| <b>Total</b>         | <b>21</b>             | <b>20</b>       | <b>12</b>                        | <b>53</b>   |

<sup>1</sup> concurrently scored items (language and behaviour) and observed throughout the assessment.

#### **4.1.2 Gold standard: Bayley Scales of Infant Development, 3<sup>rd</sup> Edition (BSID-III)**

The BSID-III<sup>6</sup>, considered to be the current ‘gold standard assessment’ of infant development<sup>5-7</sup>, was the measure against which the INTER-NDA was validated. Administration of the BSID-III begins at a start point based on the child’s chronological age (range = A-Q), which is adjusted for preterm delivery up until 2 years of age. If the child does not pass the first 3 items from their start point, the assessor moves to the previous start point. Based on their age bracket, all children in the current study began the BSID-III assessment at start point *M* or *N* (range = 22 months 16 days -28 months 15 days). Assessment begins when the child passes the first 3 items from a start point and continues until 5 consecutive items are failed. The full BSID-III consists of 326 items (some of which are timed), requires a number of trials, and includes both left and right administration on some items. As such, assessment can be lengthy (up to 90 minutes) and requires a complex set of assessment items (Figure 4.2). An advantage of the BSID-III, however, is that there are no floor or ceiling effects, as test administration is adjusted to reflect the child’s developmental age.



**Figure 4.2. Constituent items of the BSID-III assessment including scoring sheets**

Items on the BSID-III are grouped into a number of subscales (cognitive, expressive language, receptive language, fine motor, gross motor, behaviour and social-emotional), for which a raw score is calculated manually by the assessor (adding the scores). These are manually translated into scaled scores ( $M=10$ ,  $SD=3$ ,  $range=0-19$ ) from tables provided in the BSID-III manual<sup>6</sup>. Scaled scores are then combined into composite scores, which are derived from sums of the subtest scaled scores. Composite scores include cognitive, language, motor and social-emotional scales ( $M=100$ ,  $SD=15$ ,  $range=40-160$ ). All BSID-III scoring calculations are completed manually on the record form (Figure 4.3).

**Bayley**  
Scales of Infant and Toddler Development™  
THIRD EDITION

Child's name: Sam Weisinger  
Sex: ☒ M ☐ F ID #: 123-45-6789  
Examiner's name: Maggie Young  
School/Child care program: Royal Daycare Center  
Reason for referral: Child is mostly non-verbal

**Subtest Summary Scores**

| Subtest                        | Total Raw Score | Scaled Score | Composite Score | Percentile Rank | Conf. Interval (1.5%) |
|--------------------------------|-----------------|--------------|-----------------|-----------------|-----------------------|
| Cognitive (Cp)                 | 63              | 6            | 80              | 9               | 74-90                 |
| Language (Lang)                |                 |              |                 |                 |                       |
| Receptive Communication (RC)   | 26              | 7            |                 |                 |                       |
| Expressive Communication (EC)  | 23              | 4            |                 |                 |                       |
| Sum                            | 11              |              | 74              | 4               | 69-83                 |
| Motor (Mo)                     |                 |              |                 |                 |                       |
| Fine Motor (FM)                | 38              | 5            |                 |                 |                       |
| Gross Motor (GM)               | 59              | 8            |                 |                 |                       |
| Sum                            | 13              |              | 79              | 8               | 73-88                 |
| Social-Emotional (SE)          | 93              | 4            | 70              | 2               | 65-81                 |
| Adaptive Behavior              |                 |              |                 |                 |                       |
| *Communication (Cm)            | 28              | 4            |                 |                 |                       |
| *Community Use (CU)            | 14              | 6            |                 |                 |                       |
| *Functional Pre-Academics (FA) | 6               | 4            |                 |                 |                       |
| *Home Living (HL)              | 38              | 7            |                 |                 |                       |
| *Health and Safety (HS)        | 40              | 7            |                 |                 |                       |
| *Leisure (L)                   | 42              | 7            |                 |                 |                       |
| *Self-Care (SC)                | 51              | 5            |                 |                 |                       |
| *Self-Direction (SD)           | 35              | 4            |                 |                 |                       |
| *Social (So)                   | 41              | 5            |                 |                 |                       |
| *Motor (Mo)                    | 59              | 6            |                 |                 |                       |
| Sum                            | 55              |              | 64              | 1               | 54-69                 |

**Calculate Age and Start Point**

| Year                                           | Month | Days |
|------------------------------------------------|-------|------|
| 2004                                           | 06    | 18   |
| 2005                                           | 07    | 09   |
| Date Tested                                    |       |      |
| 2002                                           | 08    | 17   |
| Date of Birth                                  |       |      |
| Age                                            | 2     | 10   |
| Age in Months and Days                         | 24    | 10   |
| Sum = 34                                       |       |      |
| Adjustment for Prematurity                     |       |      |
| Adjusted Age                                   | 34    | 22   |
| Start Point                                    |       |      |
| Calculate start point according to chart below |       |      |

| Age                                  | Start Point |
|--------------------------------------|-------------|
| 16 days-1 month 15 days              | A           |
| 1 month 16 days-2 months 15 days     | B           |
| 2 months 16 days-3 months 15 days    | C           |
| 3 months 16 days-4 months 15 days    | D           |
| 4 months 16 days-5 months 15 days    | E           |
| 5 months 16 days-6 months 15 days    | F           |
| 6 months 16 days-8 months 15 days    | G           |
| 8 months 0 days-10 months 15 days    | H           |
| 10 months 0 days-12 months 15 days   | I           |
| 12 months 0 days-14 months 15 days   | J           |
| 14 months 16 days-16 months 15 days  | K           |
| 16 months 16 days-18 months 15 days  | L           |
| 18 months 16 days-20 months 15 days  | M           |
| 20 months 16 days-22 months 15 days  | N           |
| 22 months 16 days-24 months 15 days  | O           |
| 24 months 16 days-26 months 15 days  | P           |
| 26 months 16 days-28 months 15 days  | Q           |
| 28 months 16 days-30 months 15 days  |             |
| 30 months 16 days-32 months 15 days  |             |
| 32 months 16 days-34 months 15 days  |             |
| 34 months 16 days-36 months 15 days  |             |
| 36 months 16 days-38 months 15 days  |             |
| 38 months 16 days-40 months 15 days  |             |
| 40 months 16 days-42 months 15 days  |             |
| 42 months 16 days-44 months 15 days  |             |
| 44 months 16 days-46 months 15 days  |             |
| 46 months 16 days-48 months 15 days  |             |
| 48 months 16 days-50 months 15 days  |             |
| 50 months 16 days-52 months 15 days  |             |
| 52 months 16 days-54 months 15 days  |             |
| 54 months 16 days-56 months 15 days  |             |
| 56 months 16 days-58 months 15 days  |             |
| 58 months 16 days-60 months 15 days  |             |
| 60 months 16 days-62 months 15 days  |             |
| 62 months 16 days-64 months 15 days  |             |
| 64 months 16 days-66 months 15 days  |             |
| 66 months 16 days-68 months 15 days  |             |
| 68 months 16 days-70 months 15 days  |             |
| 70 months 16 days-72 months 15 days  |             |
| 72 months 16 days-74 months 15 days  |             |
| 74 months 16 days-76 months 15 days  |             |
| 76 months 16 days-78 months 15 days  |             |
| 78 months 16 days-80 months 15 days  |             |
| 80 months 16 days-82 months 15 days  |             |
| 82 months 16 days-84 months 15 days  |             |
| 84 months 16 days-86 months 15 days  |             |
| 86 months 16 days-88 months 15 days  |             |
| 88 months 16 days-90 months 15 days  |             |
| 90 months 16 days-92 months 15 days  |             |
| 92 months 16 days-94 months 15 days  |             |
| 94 months 16 days-96 months 15 days  |             |
| 96 months 16 days-98 months 15 days  |             |
| 98 months 16 days-100 months 15 days |             |

PsychCorp  
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ISBN 015502703-5

Figure 4.3. An example completed BSID-III Record Form<sup>7</sup>

The objective of this paper is to assess the validity of the INTER-NDA as an assessment of infant neurodevelopment. The aims of this study are: 1) to determine the level of agreement between the INTER-NDA and the BSID-III in the 22-28 month age group; and 2) to examine the internal consistency of the INTER-NDA.

## 4.2 Methods

### 4.2.1 Study population

Eighty-one infants (44 boys and 37 girls) aged 23.06 to 28.29 months ( $M=25.39$ ,  $SD=1.11$ ) were drawn from a sample of mothers enrolled between March 2010 and October 2012 in the Oxford Postnatal Treatment (OPT) study. The children were drawn from families residing in Oxfordshire, Buckinghamshire and Berkshire who had been referred to the OPT study

to participate in a treatment trial for clinical postnatal depression. Informed consent was obtained upon enrolment to the study. Exclusion criteria included infants born <35 weeks of gestation, infants with birth weight (BW) <2000g, maternal age <18 years, severe psychiatric diagnosis other than postnatal depression, life threatening or other serious physical illness, serial illness of the infant, mother not residing with the infant, and English proficiency below conversational level. Demographic information for the mother, father/and or mother's partner and infant was obtained using questionnaire.

#### **4.2.2 Neurodevelopmental assessment procedure**

The neurodevelopmental assessment was conducted by one of 4 assessors as part of the 2 year follow-up of the OPT study. The BSID-III assessment took place in a lab-based setting to ensure standard surroundings for each assessment. Informed consent was obtained at the beginning of the assessment. The BSID-III was conducted in person at the assessment, and the INTER-NDA was assessed using video footage of the BSID-III assessment. As such, children were recording doing the BSID-III and the INTER-NDA was rated from video footage extracted from this assessment. The INTER-NDA and BSID-III assessments were thus completed for the child at the same exact age. This was necessary as the INTER-NDA contains a large subset of BSID-III items, and as such, practice effects (in either direction) would skew results.

Two assessors were present at each assessment, with one assessor responsible for administration of the BSID-III to the child, and the other conducting an interview with the mother quietly, at the other end of the same room. The assessors administering the BSID-III were trained and qualified in BSID-III administration and scoring. Children completed a shortened version of the BSID-III which included assessment on the cognitive, expressive communication, receptive communication, overall language and behaviour subscales. Full administration took approximately 60 minutes. BSID-III scoring was conducted throughout the assessment, with scaled and composite scores calculated manually by the assessor immediately



following the assessment. In line with the BSID-III scoring system, scaled scores ( $M=10$ ,  $SD=3$ ) were derived for expressive and receptive communication, and composite scores ( $M=100$ ,  $SD=15$ ) were derived for cognitive and overall language. The total behaviour score was converted to a Z-score.

The assessments were video-recorded using 3 cameras for different angles. The INTER-NDA was scored from video footage of the relevant items by an independent assessor, trained in INTER-NDA administration and scoring. Footage of administration was available for all INTER-NDA items except one, which was indirectly calculated (see details below in section 4.2.3: Calculation of the INTER-NDA item not administered as part of the BSID-III). INTER-NDA total, mean and Z-scores were calculated automatically, ensuring no calculation errors. Both the assessors of the BSID-III and INTER-NDA were blind to the scores of the other assessment.

The motor, attention and emotional-reactivity subscales of the INTER-NDA were not validated as part of this study, as these subscales are comprised entirely of existing measures, and have been validated previously<sup>8-10</sup>.

#### **4.2.3 Calculation of the INTER-NDA item not administered as part of the BSID-III**

The INTER-NDA items and corresponding BSID-III and RNDA items are presented in Tables S4.1-S4.4 for each of the subscales. One item on the INTER-NDA was not directly observable from the video recordings of the BSID-III administration. This item thus had to be indirectly calculated. The item was item 18 (maternal-report question of whether the child asks for the toilet) which is a question from the RNDA at 24 months<sup>8</sup> and at 25 to 30 months<sup>11</sup>. This item is suggested to be a good index of the infants' ability to relate language meaningfully to reality situations<sup>12</sup>. Based on observation of developmental trends, this item is considered a good discriminator of normal and delayed developmental progression between 24-30 months<sup>13</sup>. Although item 18 was indirectly calculated in the current study, cognitive scales including this

item have been previously validated against the BSID<sup>8,11</sup>, showing good inter-rater reliability ( $\kappa=0.80$ )<sup>8</sup> and good concurrent<sup>8</sup> and discriminant validity<sup>11</sup>.

Based on the above information, the child's score on this item was calculated indirectly using a multistage process. Firstly, the cognitive and language components required to complete this item were determined through consultation with experts from the INTERGROWTH-21<sup>st</sup> Infant Development Group<sup>14</sup>. These were determined as Q-level items (which include cognitive abilities such as 'imitating two-step action' and 'demonstrating imaginary play'), with item completion requiring abilities such as posing multiple-word questions (item 32: level Q) and using future tense (item 48: level Q). Therefore, if the child completed the INTER-NDA equivalent questions to those that are level Q on the BSID-III (INTER-NDA items 3, 4 and 13, corresponding to BSID-III items 68, 70 and 71, respectively), they were given a score of "Occasionally" (3 out of a total of 4 points) for item 18 on the INTER-NDA. As this method is deductive, it cannot be assumed that the child "Always" asks for the toilet, and as such, the maximum a child could score on this item was "Occasionally". If the child did not score maximum points on items 3, 4 and 13 on the INTER-NDA, it was assumed that the child was not at the cognitive competency level to complete INTER-NDA item 18, and the child thus scored "Never" (1 out of a total of 4 points) on item 18. The calculations for this item are presented in Tables S4.5-S4.6 with equations below.

$$IF \Sigma(3, 4, 13) = 12, THEN \text{item } 18 = 3$$

$$IF \Sigma(3, 4, 13) < 12, THEN \text{item } 18 = 1$$

#### 4.2.4 Statistical analysis

The total and mean INTER-NDA scores for each of the subscales were converted to Z-scores, and were assessed against the corresponding BSID-III subscales. Difference scores between BSID-III and INTER-NDA Z-scores (BSID-III *minus* INTER-NDA) were also calculated. The distributions of scores were graphed using histograms (Figure S4.1). All scores were normally distributed with the exception of the behaviour scores, as is usual with observer-report of child behaviour, which showed a positive skew (more children scoring as well behaved than poorly behaved). Multistage statistical testing recommended by Lee<sup>15</sup> and Bland and Altman<sup>16</sup> were followed to assess the validity of the INTER-NDA in six steps:

1. **Within-subject comparison of INTER-NDA and BSID-III scores:** Within-subjects repeated measures *t*-tests (for normally distributed data) and Wilcoxon signed-rank tests (for non-normally distributed data) were conducted to assess whether there was a difference between scores on the INTER-NDA and the BSID-III within subjects.
2. **Correlation between INTER-NDA and BSID-III scores:** To quantify the strength of the association between INTER-NDA and BSID-III scores, single measure intraclass correlation coefficients (ICCs) for absolute agreement were calculated for each of the subscales, using a two-way mixed effects model<sup>a</sup>.
3. **Assessment of systematic bias and limits of agreement between INTER-NDA and BSID-III scores:** Bias and limits of agreement statistics<sup>b</sup> were calculated according to the method proposed by Bland and Altman<sup>16</sup>.
4. **Systematic differences between INTER-NDA and BSID-III scores:** To identify whether the INTER-NDA scores differed systematically across different levels of the

<sup>a</sup> Two-way model allows variability among raters to be included as a second source of variability. Mixed-effects refers to the fact that there are a set number of raters (fewer than the total number of ratings).

<sup>b</sup> The bias score quantifies the difference in score likely to arise between the BSID-III and the INTER-NDA and is used for identifying when one assessment may score a child systematically lower or higher than another assessment. The limits of agreement (calculated using the standard deviation of the difference between the scores) identify the range within which 95% of the differences will lie (confidence interval at  $p < .05$ ).

BSID-III, the difference score was plotted against the BSID-III score (Bland-Altman plots), and linear regression analyses of the relationship between difference score and BSID-III score were conducted for each of the subscales<sup>c</sup>.

5. **Ability of INTER-NDA to predict low scores on BSID-III:** Scores were dichotomized into low (<1SD) and very low (<2SD) on the INTER-NDA, and borderline (<85) and extremely low (<70) on the BSID-III. Predictive properties of sensitivity and specificity were calculated to assess the ability of low and very low INTER-NDA scores to predict borderline and extremely low composite BSID-III scores, respectively. Cohen's kappa was used to determine the level of agreement between INTER-NDA and BSID-III classifications.
6. **Internal consistency of the INTER-NDA:** Finally, to assess the internal consistency of the INTER-NDA, Cronbach's alphas<sup>17</sup> were calculated for each of the subscales.

### 4.3 Results

Eighty-one infants (44 boys and 37 girls) aged 23.1 to 28.3 months ( $M=25.4$ ,  $SD=1.1$ ), completed both the INTER-NDA and the BSID-III. The mean maternal age was 31.88 years ( $SD=5.46$ ), 91% of mothers ( $n=73$ ) had an education level of GSCE (A\*-C) and above, and 98% were married or cohabiting ( $n=79$ ). The children had a mean BW of 3539g ( $SD=543g$ ) and a mean GA at birth of 39<sup>+6</sup> weeks ( $SD=1^{+4}$ ). Further demographic information is presented in Table 4.3.

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<sup>c</sup> A statistically significant association indicates systematic variation of the difference between scores across BSID-III scores.

**Table 4.3. Sample maternal, demographic, family and child characteristics**

| Variable (N)                         | n  | %    |
|--------------------------------------|----|------|
| <b>Maternal education (80)</b>       |    |      |
| <GSCE                                | 2  | 2.5  |
| GSCE (D-G)                           | 4  | 5.0  |
| GSCE (A*-C)                          | 18 | 22.5 |
| A-level                              | 8  | 10.0 |
| Professional diploma                 | 4  | 5.0  |
| Foundation degree                    | 6  | 7.5  |
| Undergraduate degree                 | 23 | 28.7 |
| Master's degree                      | 10 | 12.5 |
| Doctoral degree                      | 5  | 6.3  |
| <b>Maternal age at delivery (80)</b> |    |      |
| ≤19                                  | 1  | 1.3  |
| 20-35                                | 60 | 75.0 |
| >35                                  | 19 | 23.8 |
| <b>Marital status (80)</b>           |    |      |
| Single                               | 6  | 7.5  |
| Relationship - non-cohabiting        | 1  | 1.3  |
| Relationship - cohabiting            | 73 | 91.3 |
| <b>Maternal employment (80)</b>      |    |      |
| Unemployed                           | 26 | 32.5 |
| Student                              | 1  | 1.3  |
| Maternity leave                      | 47 | 58.8 |
| Part time                            | 4  | 5.0  |
| Full time                            | 2  | 2.5  |
| <b>Parents co-reside (80)</b>        |    |      |
| Yes                                  | 69 | 86.3 |
| No                                   | 11 | 13.8 |
| <b>Partner education (75)</b>        |    |      |
| <GSCE                                | 2  | 2.7  |
| GSCE (D-G)                           | 4  | 5.3  |
| GSCE (A*-C)                          | 12 | 16.0 |
| A-level                              | 19 | 25.3 |
| Professional diploma                 | 0  | 0.0  |
| Foundation degree                    | 5  | 6.7  |
| Undergraduate degree                 | 18 | 24.0 |
| Master's degree                      | 7  | 9.3  |
| Doctoral degree                      | 8  | 10.7 |
| <b>Parity (79)</b>                   |    |      |
| 1                                    | 40 | 50.6 |
| >1                                   | 39 | 49.4 |
| <b>Child Sex (81)</b>                |    |      |
| Male                                 | 44 | 54.3 |
| Female                               | 37 | 45.7 |
| <b>Mode of delivery (73)</b>         |    |      |
| Normal                               | 51 | 69.9 |
| Cesarean section                     | 22 | 30.1 |
| <b>Birth weight (80)</b>             |    |      |
| <2500g                               | 2  | 2.5  |
| ≥2500g                               | 78 | 97.5 |
| <b>Preterm delivery (80)</b>         |    |      |
| <37 weeks                            | 3  | 3.8  |
| ≥37 weeks                            | 77 | 96.3 |
| <b>Breastfeeding duration (62)</b>   |    |      |
| Never                                | 2  | 3.2  |
| <6 months                            | 47 | 75.8 |
| ≥6 months                            | 13 | 21.0 |
| <b>Admitted to SCBU (80)</b>         |    |      |
| Yes                                  | 4  | 5.0  |
| No                                   | 76 | 95.0 |

GSCE=General Certificate of Secondary Education; SCBU=special care baby unit

Means and SDs for the subscales scores of the INTER-NDA and BSID-III are presented in Table 4.4. On the INTER-NDA, the mean cognitive score was 36.81 ( $SD=6.50$ ), overall language was 37.20 ( $SD=7.27$ ) and behaviour was 17.54 ( $SD=3.37$ ). On the BSID-III, the mean cognitive composite score was 98.83 ( $SD = 13.09$ ), overall language was 100.86 ( $SD=17.33$ ) and behaviour was 33.48 ( $SD = 4.56$ ).

**Table 4.4. Mean total score (SD) of INTER-NDA and BSID-III subscales**

| Subscale                          | INTER-NDA (N=81) | BSID-III (N=81)             |
|-----------------------------------|------------------|-----------------------------|
| Cognitive                         | 36.81 (6.50)     | 98.83 (13.09) <sup>i</sup>  |
| Receptive language/communication  | 6.21 (1.19)      | 10.04 (2.96) <sup>ii</sup>  |
| Expressive language/communication | 30.99 (6.55)     | 10.20 (3.29) <sup>ii</sup>  |
| Overall language                  | 37.20 (7.27)     | 100.86 (17.33) <sup>i</sup> |
| Positive behaviour                | 12.54 (2.48)     | 23.00 (3.36) <sup>iii</sup> |
| Negative behaviour                | 4.94 (1.06)      | 10.48 (1.39) <sup>iii</sup> |
| Overall Behaviour                 | 17.54 (3.37)     | 33.48 (4.56) <sup>iii</sup> |

<sup>i</sup> Composite scores; <sup>ii</sup> scaled scores; <sup>iii</sup> total raw scores

Within subjects *t*-tests and Wilcoxon signed-rank tests revealed that there were no differences in BSID-III and INTER-NDA scores across all subscales (Table 4.5).

**Table 4.5. Within-subjects *t*-tests and Wilcoxon signed-rank tests comparing total and mean/median scores of the INTER-NDA and BSID-III**

| Subscale                          | Total Score              | Mean Score               |
|-----------------------------------|--------------------------|--------------------------|
| Cognitive                         | $t(80) = 0.42, p = .67$  | $t(80) = 0.88, p = .38$  |
| Receptive language/communication  | $t(80) = 0.00, p = 1.00$ | $t(80) = 0.00, p = 1.00$ |
| Expressive language/communication | $t(80) = 0.00, p = 1.00$ | $t(80) = 0.00, p = 1.00$ |
| Overall language                  | $t(80) = 1.08, p = .28$  | $t(80) = 1.08, p = .28$  |
| Behaviour <sup>a</sup>            | $Z = -0.64, p = .52$     | $Z = -0.64, p = .52$     |
| Positive Behaviour <sup>a</sup>   | $Z = -0.01, p = .99$     | $Z = -0.01, p = .99$     |
| Negative Behaviour <sup>a</sup>   | $Z = -0.43, p = .67$     | $Z = -0.43, p = .67$     |

<sup>a</sup> Wilcoxon signed-rank test for non-normally distributed data

The ICCs for the BSID-III and INTER-NDA subscales are presented in Table 4.6. They indicate a strong association between all INTER-NDA subscales and the BSID-III equivalents.

**Table 4.6. Intraclass correlation coefficient, *r* (95% CI), of association between the INTER-NDA and BSID-III total and mean scores**

| Subscale                          | Total Score     | Mean Score      |
|-----------------------------------|-----------------|-----------------|
| Cognitive                         | .80 (.70-.86)** | .85 (.77-.90)** |
| Receptive language/communication  | .75 (.63-.83)** | .75 (.63-.83)** |
| Expressive language/communication | .88 (.82-.92)** | .88 (.82-.92)** |
| Overall language                  | .88 (.83-.92)** | .88 (.83-.92)** |
| Positive Behaviour                | .84 (.77-.90)** | .84 (.77-.90)** |
| Negative Behaviour                | .78 (.67-.85)** | .78 (.67-.85)** |
| Overall Behaviour                 | .88 (.82-.92)** | .88 (.82-.92)** |
| Overall                           | .83 (.75-.89)** | .84 (.76-.89)** |

\*\* $p < .001$

All INTER-NDA subscales fell within the limit of acceptability for the lower limit of the ICC confidence interval proposed by Bland and Altman<sup>16</sup> (greater than .70), with the exception of receptive language and negative behaviour for which the ICCs are good given that each of these subscales had only two items each (.75 and .78 respectively). Figure 4.4 depicts the association between BSID-III scores and INTER-NDA Z-scores for all subscales.



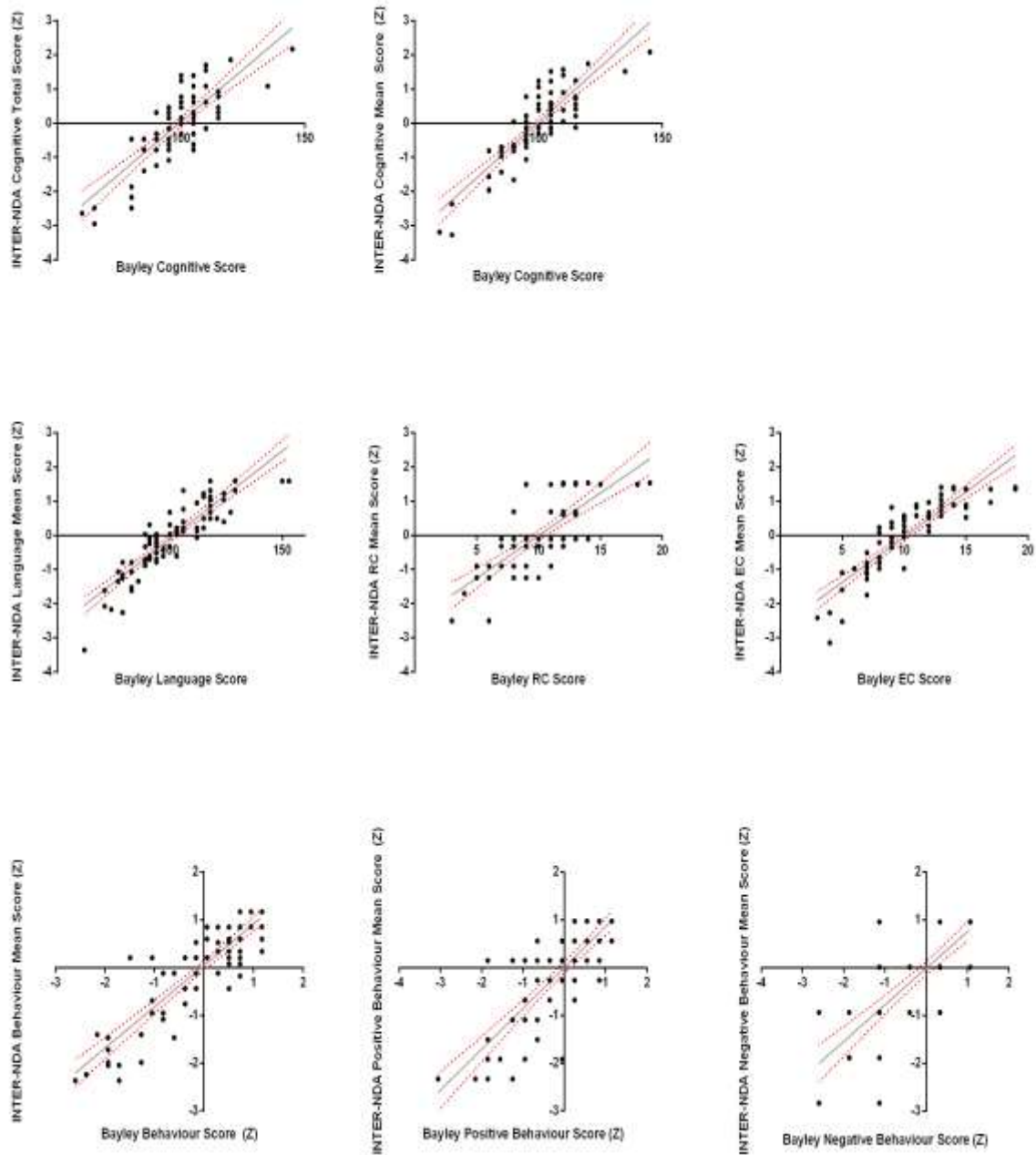


Figure 4.4. Association between BSID-III scores and INTER-NDA scores. Grey solid line = regression line; Red dotted line = 95% confidence interval of regression line.

The Bland-Altman analysis indicated no, or very low bias in all subscales (Table 4.7), suggesting that there is very little difference between the scores obtained on the INTER-NDA compared to the BSID-III. To aid interpretation, the bias and limits of agreements values were converted to standardized BSID-III composite score equivalents ( $M=100$ ,  $SD=15$ ) for low, average and high INTER-NDA scores (Table S4.7). All INTER-NDA mean scores ( $Z\text{-score} = 0$ ) correspond to a BSID-III composite score in the range of 99-101.

**Table 4.7. Bland-Altman analysis of bias and limits of agreement between subscale scores of the INTER-NDA and BSID-III**

| Subscale                          | Bias   | Lower limit of agreement | Upper limit of agreement |
|-----------------------------------|--------|--------------------------|--------------------------|
| Cognitive (Total)                 | .031   | -1.122                   | 1.291                    |
| Cognitive (Mean)                  | .054   | -1.024                   | 1.132                    |
| Receptive language/communication  | .000   | -1.401                   | 1.401                    |
| Expressive language/communication | .000   | -0.962                   | 0.962                    |
| Overall Language                  | .057   | -0.892                   | 1.006                    |
| Positive Behaviour                | -0.008 | -1.127                   | 1.111                    |
| Negative Behaviour                | .001   | -1.337                   | 1.339                    |
| Overall Behaviour                 | -0.052 | -1.033                   | 0.924                    |

The Bland-Altman plots and linear regression analyses of the difference scores (BSID-III *minus* INTER-NDA) are presented in Table 4.8 and in Figure 4.5. Weak but significant positive associations were identified in all scales, such that variation in BSID-III score accounted for 7.2% of the difference between the BSID-III and INTER-NDA score in the cognitive subscale, 13.4% in the receptive language subscale, 6.7% in the expressive language subscale, 5.1% in the overall language subscale, 7.6% of the total behaviour subscale, 6.6% of the positive behaviour subscale and 12.2% of the negative behaviour subscale. This suggests that there is some systematic

variation of the difference between scores across BSID-III scores, such that at higher BSID-III scores, there are bigger differences between the INTER-NDA and the BSID-III.

**Table 4.8. Regression coefficients of the association between difference scores (Z-score BSID-III minus Z-score INTER-NDA) and BSID-III scores**

| Subscale                          | <i>r</i> | <i>p</i> |
|-----------------------------------|----------|----------|
| Cognitive (Total)                 | .31      | .005*    |
| Cognitive (Mean)                  | .27      | .016*    |
| Receptive language/communication  | .37      | .001*    |
| Expressive language/communication | .26      | .020*    |
| Overall language                  | .23      | .042*    |
| Positive Behaviour                | .26      | .020*    |
| Negative Behaviour                | .35      | .001*    |
| Overall Behaviour                 | .28      | .013*    |

\* $p < .05$ ; \*\* $p < .001$

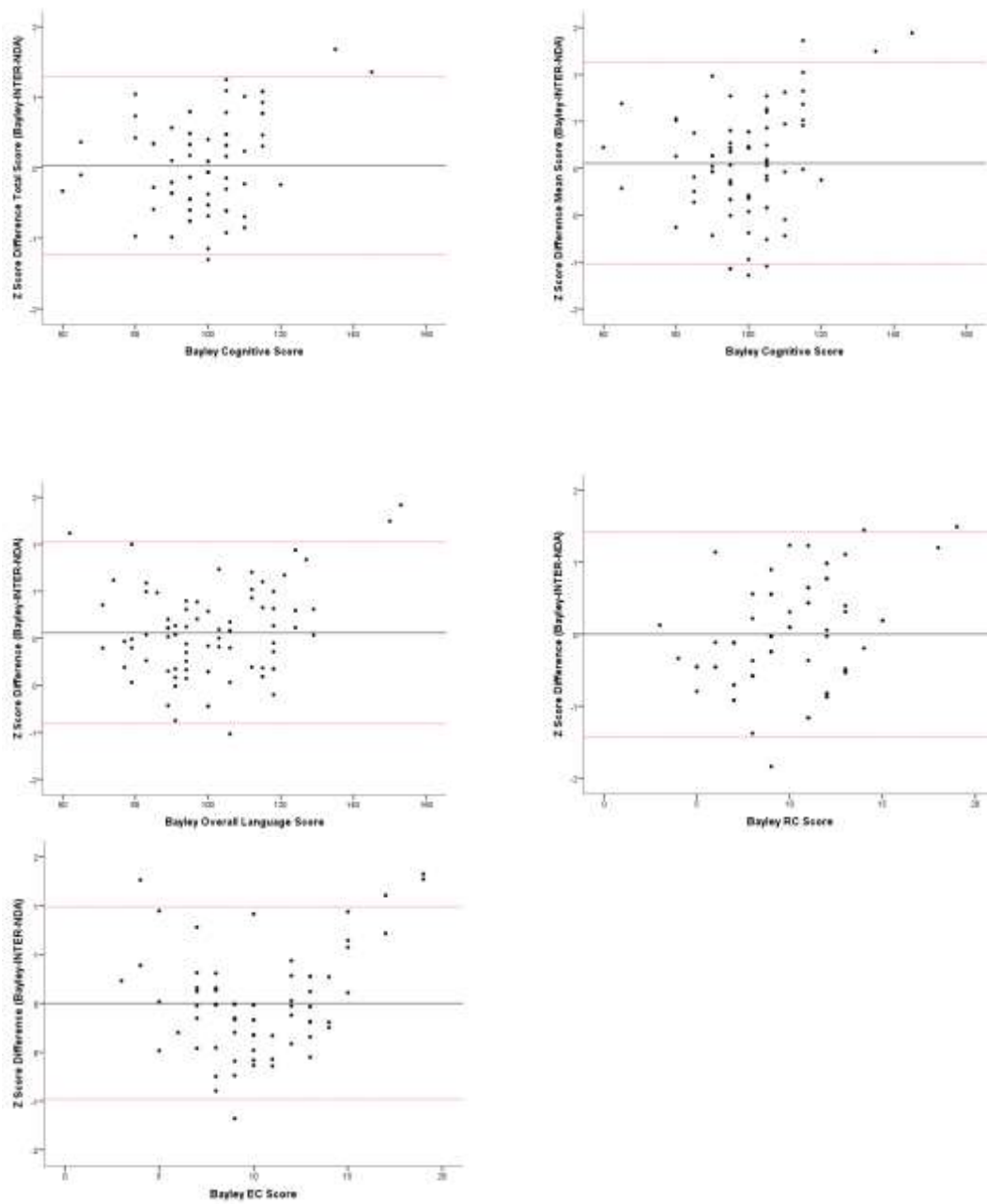


Figure 4.5. Bland-Altman plots of the difference in BSID-III and INTER-NDA scores across the range of BSID-III scores

Predictive properties were calculated for the ability of low (<1SD) and very low (<2SD) INTER-NDA scores to predict borderline (<85) and extremely low (<70) composite BSID-III scores. For low INTER-NDA cognitive scores (<1SD: Table 4.9), sensitivity was moderate (54-67%) and specificity was high (99%), with moderate agreement between INTER-NDA and BSID-III classifications ( $\kappa=0.63-0.72$ ,  $p<.001$ ). For low INTER-NDA language score, both sensitivity and specificity was high (92-97%) with good agreement between INTER-NDA and BSID-III classifications ( $\kappa=0.87$ ,  $p<.001$ ).

**Table 4.9. Number of low (<1SD) and borderline (<85) cognitive and language scores on the INTER-NDA and BSID-III, sensitivity, specificity and agreement between scales (Cohen's kappa)**

| INTER-NDA                | BSID-III <85 | BSID-III $\geq 85$ | Sensitivity | Specificity | $\kappa$ |
|--------------------------|--------------|--------------------|-------------|-------------|----------|
| <b>Cognitive (Total)</b> |              |                    |             |             |          |
| <1SD                     | 6            | 5                  | 54.5%       | 98.6%       | 0.63**   |
| $\geq 1SD$               | 1            | 69                 |             |             |          |
| <b>Cognitive (Mean)</b>  |              |                    |             |             |          |
| <1SD                     | 6            | 3                  | 66.7%       | 98.6%       | 0.72**   |
| $\geq 1SD$               | 1            | 71                 |             |             |          |
| <b>Overall language</b>  |              |                    |             |             |          |
| <1SD                     | 12           | 1                  | 92.3%       | 97.1%       | 0.87**   |
| $\geq 1SD$               | 2            | 66                 |             |             |          |

\* $p<.05$ ; \*\* $p<.001$

For very low INTER-NDA cognitive scores (<2SD; Table 4.10), sensitivity was moderate (60%) for cognitive total score, and high (100%) for cognitive mean score. Specificity was high for both cognitive scores (100%), with good agreement between INTER-NDA and BSID-III classifications ( $\kappa=0.74-1.00$ ,  $p<.001$ ). For low INTER-NDA language score, sensitivity was low (25%), although specificity was high (100%) with fair agreement between INTER-NDA and BSID-III classifications ( $\kappa=0.39$ ,  $p<.001$ ).

**Table 4.10. Number of low (<2SD) and extremely low (<70) cognitive and language scores on the INTER-NDA and BSID-III, sensitivity, specificity and agreement between scales (Cohen's kappa)**

| INTER-NDA                | BSID-III <70 | BSID-III ≥70 | Sensitivity | Specificity | κ      |
|--------------------------|--------------|--------------|-------------|-------------|--------|
| <b>Cognitive (Total)</b> |              |              |             |             |        |
| <2SD                     | 3            | 2            | 60.0%       | 100.0%      | 0.74** |
| ≥2SD                     | 0            | 76           |             |             |        |
| <b>Cognitive (Mean)</b>  |              |              |             |             |        |
| <2SD                     | 3            | 0            | 100.0%      | 100.0%      | 1.00** |
| ≥2SD                     | 0            | 78           |             |             |        |
| <b>Overall language</b>  |              |              |             |             |        |
| <2SD                     | 1            | 3            | 25.0%       | 100.0%      | 0.39** |
| ≥2SD                     | 0            | 77           |             |             |        |

\*p&lt;.05; \*\*p&lt;.001

To assess internal consistency, Cronbach's alphas were calculated, presented in Table 4.11. The alphas were good for the cognitive, receptive language, expressive language, fine motor and positive behaviour subscales of the INTER-NDA and were acceptable the gross motor and negative behaviour subscales. The corresponding internal consistencies of the BSID-III, calculated from the OPT data, are also presented in this table for comparison.

**Table 4.11. Cronbach's alphas to assess internal consistency of the INTER-NDA and BSID-III for each of the subscales**

| Subscale                          | INTER-NDA | BSID-III |
|-----------------------------------|-----------|----------|
| Cognitive                         | .811      | .877     |
| Receptive language/communication  | .827      | .890     |
| Expressive language/communication | .895      | .925     |
| Overall language                  | .863      | .948     |
| Positive Behaviour                | .846      | .819     |
| Negative Behaviour                | .563      | .619     |
| Overall Behaviour                 | .902      | .869     |
| Fine motor <sup>i</sup>           | .787      | -        |
| Gross motor <sup>i</sup>          | .666      | -        |

<sup>i</sup>Fine and gross motor subscales were not administered in the BSID-III assessment

#### 4.4 Summary of results

The INTER-NDA is a multi-dimensional neurodevelopment assessment tool, designed for use in the 22-28 month age group. The purpose of this study was to evaluate the performance of the INTER-NDA against the BSID-III, and to present the psychometric properties of the tool.

The results indicate that the INTER-NDA shows strong agreement with the BSID-III for children in the 22-28 month age group. No within-subject differences were between the INTER-NDA and BSID scores, and ICCs showed strong associations between cognitive, language and behaviour subscales on the INTER-NDA subscales and the BSID-III subscales. The results of the Bland-Altman analysis confirm the agreement between the INTER-NDA and BSID-III by showing that a child with a mean cognitive score on the INTER-NDA is likely to score 101 on the cognitive composite score of the BSID-III, with a 95% probability that the true value of their score will fall in the range of 85-118. Given that the SD of the BSID-III composite score is 15, the results indicate that 95% of the children scoring at the mean of the INTER-NDA will fall within 1SD below and just over 1SD above the BSID-III mean, providing evidence that the two scales are functioning

similarly from a statistical and distributional point of view. These results indicate that the likelihood of a child scoring above or below 1SD of the BSID-III mean, when he/she achieves a mean score on the INTER-NDA, is statistically negligible.

The Bland-Altman plots and linear regression analyses of the difference scores in the INTER-NDA across different levels of the BSID-III score (Figures 3a-3e; Table 7) reveal that at the extremely low limits of the BSID-III, children scored relatively higher on the INTER-NDA (floor effect) and at the extremely high limits of the BSID-III, children scored relatively lower on the INTER-NDA (ceiling effect). This finding reflects the differences in the age-range that the tests were designed to assess i.e. while the INTER-NDA items are specific to the 22-28 month age group, in the BSID-III, test administration may begin at a lower level than that indicated by the child's age range and continues until the child fails 5 consecutive items (at times much beyond the child's chronological age). This finding therefore suggests that the INTER-NDA functions well in agreement to the BSID-III in the 22-28 month age group.

The ability of low and very low INTER-NDA scores to predict borderline and extremely low BSID-III scores, respectively, shows good specificity across all classifications. More than 97% of children who scored in the normal range of the INTER-NDA (<1SD below mean) also scored in the normal range in the BSID ( $\geq 85$ ). This is important, given that the INTER-NDA was designed as a screening tool for neurodevelopment, as it suggests that few children who are 'missed' by the INTER-NDA will have borderline or lower scores on the BSID-III. Predictive properties were particularly strong for very low cognitive (mean) INTER-NDA scores (<2SD), which predicted extremely low BSID-III scores (<70) with 100% sensitivity and 100% specificity. Cognitive (total) (<1SD) and overall language (<2SD) had low sensitivity compared to the other domains, 55% and 25%, respectively. For the cognitive (total) score, this may be due to the fact that the cognitive (total) score does not account for items that were non-assessable, and thus is a less sensitive measure than cognitive (mean) score. This suggests that caution should be taken drawing



conclusions from these cut-off points in these domains. For the overall language score, the restricted number of items (due to the targeted age range) may introduce floor effects for those children than have very poor language development.

The internal consistency of the subscales of the INTER-NDA are comparable with those of the BSID-III for the 22-28 month age group, despite the INTER-NDA having less than a fifth of the number of items compared with the BSID-III, and taking less than a fifth of the time it takes to administer a complete BSID-III. The findings of this study add to the psychometric property evaluations that have already been conducted for the INTER-NDA, with full current psychometric data, including that of this study, presented in Table 4.12.

**Table 4.12. Currently and previously reported psychometric properties of the INTER-NDA**

| Psychometric property | Description                                                                                                                                                 | Score                                                                                                                               | Comment                                                                                                                                                                                                                   |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Reliability</b>    |                                                                                                                                                             |                                                                                                                                     |                                                                                                                                                                                                                           |
| Internal consistency  | Evaluates the similarity of test items assessed in one domain                                                                                               | Analysis presented in Table 4.11                                                                                                    | A good level of internal consistency for the cognitive, receptive language, expressive language, fine motor and positive behaviour subscales and an acceptable level for the gross motor and negative behaviour subscales |
| Inter-observer        | Evaluates variability between different assessors on the same subject                                                                                       | $k=0.70$ 95%CI=0.47-0.88 <sup>2</sup>                                                                                               | Good inter-observer reliability. Suggests there are not systematic errors specific to a particular group of assessors                                                                                                     |
| Intra-observer        | Evaluates variability within a single assessor on a single subject                                                                                          | $k=0.79$ 95%CI=0.48-0.96 <sup>2</sup>                                                                                               | Good intra-observer reliability. Suggests assessors are reliably and objectively able to assess subjects abilities                                                                                                        |
| <b>Validity</b>       |                                                                                                                                                             |                                                                                                                                     |                                                                                                                                                                                                                           |
| Content               | Experts in the field make consensus agreement on whether the individual item and the range of items adequately sample and represent the domain of interest. | Yes. See Fernandes <i>et al.</i> (2014) for details <sup>2</sup>                                                                    | Subjective measure that cannot be used in isolation to evaluate validity                                                                                                                                                  |
| Concurrent            | Evaluates the ability of a test for predicting scores on a 'gold standard' assessment that has already been validated                                       | Analysis presented in Tables 4.9-4.10                                                                                               | Good agreement between classification from INTER-NDA scores and the 'gold standard' classification (BSID-III), with moderate sensitivity and high specificity                                                             |
| Criterion             | Ideally assessed by comparison to an established 'gold standard' test assessing the same construct                                                          | Analysis presented in Table 4.5-4.7                                                                                                 | Good criterion validity for all INTER-NDA subscales, as indicated by strong agreement with 'gold standard' assessment (BSID-III)                                                                                          |
| Construct             | Statistical evaluation to see whether values of observed data fit a theoretical model of the constructs (confirmatory factor analysis)                      | Fit indices: $\chi^2 = 38.38$ , $p < 0.001$ ; Tucker Lewis Index = .949; Comparative Fit Index = 0.964; RMSEA = 0.114 <sup>18</sup> | Theoretical model supported that all INTER-NDA domains load on to a unidimensional 'neurodevelopment' construct.                                                                                                          |

k=Cohen's kappa; RMSEA=Root mean square error of approximation

#### **4.5 Strengths and limitations of this validation study**

This study provides evidence of the validity of the INTER-NDA in assessing cognitive, language and behavioural components of early childhood development. This is important because the motivation behind the development of the tool was to overcome the dependence on time and infrastructure in the universal measurement of early childhood development, by providing a validated, objective assessment that is rapid, reliable and easy to administer in both high- and low-income settings. The use of such a measure might provide a useful, scalable solution to the challenge of early detection of neurodevelopmental impairments by shifting the emphasis of delivery channels from time-intensive in-depth assessments, to rapid, easy to administer assessment tools. The INTER-NDA is currently in use in the INTERGROWTH-21<sup>st</sup> Project study sites in Brazil, India, Italy, Kenya and the UK where more than 1000 children have been assessed to date<sup>2</sup>. The instrument is copyrighted to the University of Oxford and available in the public domain at [www.intergrowth-21st.org.uk](http://www.intergrowth-21st.org.uk).

There are some limitations however, which must be considered. One limitation of the current study is that the children were drawn from the OPT trial and therefore were exposed to maternal postnatal depression at some stage during their infancy (assessment was conducted at the end of the treatment trial), which in itself might bias the sample. However, it is unlikely that this would affect the validation results, as low-scorers on the BSID-III would be expected to score low on the INTER-NDA as well. The study was also limited in that the sample was drawn from a UK-based, highly educated population and carried out in English, despite the INTER-NDA being designed for use in geographically and culturally diverse settings. Thirdly, the OPT trial did not measure fine motor and gross motor domains on the BSID-III, and hence the validation of the motor domains of the INTER-NDA was not carried out as part of this study. Finally, although the INTER-NDA was designed to be administered and scored by the same assessor, in this study the INTER-NDA was scored from video-recordings where the person administering the tasks is

different from the person scoring the child. As such, the INTER-NDA in this study was not administered in accordance with its original design, which may potentially impact the results.

#### **4.6 Conclusion**

This study has validated the INTER-NDA against the BSID-III. The results provided evidence of a strong agreement between the INTER-NDA and the BSID-III in assessing cognition, language (receptive, expressive and overall language) and behaviour (positive, negative and overall behaviour) in the 22-28 month age group. The agreement between the INTER-NDA and the BSID-III suggests the INTER-NDA is a valid tool to for early childhood development screening and surveillance in population-based studies. It will thus be included as the assessment of cognition and attention for the INTERGROWTH-21<sup>st</sup> cohort in Chapters 5, 6 and 7 of this thesis.

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## **5 The association between birth anthropometric indices and attention and cognition in childhood**

### **Chapter outline**

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## **5.1 Introduction**

The systematic review (Chapter 2), showed that impaired fetal growth is associated with attention and cognitive impairment in childhood, and that stunting and wasting are associated with greater neurodevelopment deficit, compared to confirmation of impaired fetal growth by birth weight (BW) indicators alone. This chapter aims to test this directly (addressing the third aim of this thesis), by examining the association between 4 different indices of impaired fetal growth (specifically BW, stunting, wasting or asymmetry) and attention and cognitive development in childhood (ages 2-6). These associations will be tested in three cohorts - the 2004 Pelotas birth cohort, the ALSPAC cohort and the INTERGROWTH-21<sup>st</sup> cohort. The attention and cognitive assessments used include the CBCL, SDQ, WPPSI-R and INTER-NDA (which was validated against the BSID-III in Chapter 4).

### **5.1.1 Hypotheses**

Based on previous research, it is hypothesised that:

1. Stunting and wasting at birth will be more strongly associated with poorer attention and cognitive outcomes in childhood than BW indices alone.
2. Stunting will be more strongly associated with poorer attention and cognitive outcomes in childhood than wasting.

As there has been very little previous research examining the effect of asymmetry at birth using these indices, the asymmetry analysis is exploratory.

## **5.2 Methods**

### **5.2.1 Sample characteristics**

Three cohorts were included in the analysis, the Pelotas 2004 Birth Cohort, the ALSPAC birth cohort, and the INTERGROWTH-21<sup>st</sup> cohort. In each cohort, all children for whom at least one birth anthropometric index and attention or cognitive outcomes were available were

included in the analysis. Information is presented on each of the cohorts in Chapter 3 (sections 3.1-3.3).

### 5.2.2 Primary measures

This analysis uses birth anthropometric indices for which data was available in each of the cohorts. Birth indices are divided into the following measures:

- a) **BW indices:** LBW; SGA<sup>1</sup>; BW<10<sup>th</sup> percentile by MGRS standards<sup>2</sup>; BW<10<sup>th</sup> percentile by INTERGROWTH-21<sup>st</sup> standards<sup>3</sup>.
- b) **Stunting indices:** BL<10<sup>th</sup> percentile by MGRS standards<sup>2</sup>; BL<10<sup>th</sup> percentile by INTERGROWTH-21<sup>st</sup> standards<sup>3</sup>; HC <10<sup>th</sup> percentile by MGRS standards<sup>4</sup>; HC<10<sup>th</sup> percentile by INTERGROWTH-21<sup>st</sup> standards<sup>3</sup>.
- c) **Wasting indices:** PI<10<sup>th</sup> percentile; PI-for-gestational-age<10<sup>th</sup> percentile; BMI<10<sup>th</sup> percentile; BMI-for-age<10<sup>th</sup> percentile
- d) **Asymmetry indices:** HC/BL>90<sup>th</sup> percentile; HC/PI>90<sup>th</sup> percentile; HC/BMI>90<sup>th</sup> percentile.

Information on birth anthropometric measurements and how these indices were derived is presented in Chapter 3 (sections 3.1.2, 3.2.2, 3.3.2 and 3.4).

Follow-up assessments of attention include the CBCL at 24 months in the INTERGROWTH-21<sup>st</sup> cohort, the CBCL at 48 months in the Pelotas cohort, and the SDQ at 81 months in the ALSPAC cohort. Follow-up assessments of cognition include the INTER-NDA at 24 months in the INTERGROWTH-21<sup>st</sup> cohort, and the WPPSI-R at 48 months in the Pelotas cohort and at 49 months in the ALSPAC cohort. More information on the attention and cognitive assessment procedures are presented in Chapter 3 (Sections 3.1.2, 3.2.2, and 3.3.2).



### 5.2.3 Confounding variables

Data was collected on a range of demographic, maternal, gestational, perinatal, and childhood variables (such as maternal education, illness during pregnancy, APGAR scores, duration of breastfeeding etc.). More information on the collection and classification of confounding variables is presented in Chapter 3 (sections 3.2.1, 3.2.3 and 3.3.3).

### 5.2.4 Statistical analysis

#### 5.2.4.1 Outcome variables

Primary analyses preserved the attention problem scores (CBCL; SDQ) as continuous outcomes (whereby a higher attention syndrome score reflects greater attention impairment), as accumulating evidence suggests attention problems may lie on a continuous dimension<sup>5,6</sup>. Cognitive outcomes using the INTER-NDA and the WPPSI-R were converted to Z-scores (calculated by site for the INTER-NDA) and grouped by SD, in order to preserve the ordinal nature of the outcome for ordinal logistic regression, and in accordance with previous publications<sup>7,8</sup>. A lower cognitive score reflects greater cognitive impairment.

#### 5.2.4.2 Statistical analyses

1. **Attrition:** Differences in sample characteristics between the sample and those lost-to-follow up were assessed using univariate ANOVAs, Pearson  $\chi^2$  tests and  $\chi^2$  tests for linear trend.
2. **Prevalence comparisons:** The prevalence of birth anthropometric indices and attention and cognitive impairments were calculated for each cohort. Cross-cohort comparison of the frequency distributions were conducted using chi-squared analyses.
3. **Relationships between exposure variables and outcome variables:** The relationship between the birth anthropometric indices and between attention and cognitive scores were assessed using bivariate correlations.

4. **Between-group comparisons:** Mean and SDs of attention and cognitive scores by each birth anthropometric index (dichotomised) was calculated for each cohort. Attention and cognitive scores by birth anthropometric indices were compared using Kruskal-Wallis tests for attention outcomes and one-way ANOVAs for cognitive outcomes. Boxplots (attention outcomes) and Levene's tests (cognitive outcomes) were used to assess homogeneity of variance.
5. **Distribution and associations of confounding variables:** The frequency distribution of potential confounding maternal and child variables were calculated for each cohort, and associations between confounding variables and attention and cognitive scores were assessed using univariable ordinal logistic regression (OLR)<sup>d</sup>.
6. **Hierarchical OLR modelling (continuous outcome):** The primary analysis to examine the associations between birth anthropometric indices and attention and cognitive outcomes consisted of hierarchical modelling using OLR, a common statistical approach in epidemiological studies of childhood impairments/illness<sup>9</sup>. Firstly, unadjusted associations between birth anthropometric indices and attention/cognitive outcomes (univariable OLR) were examined (adjusting only for age of child at assessment). These unadjusted models were then successively adjusted for potential confounders (multivariable OLR) that may affect either the exposure (birth anthropometric measure) or outcome (childhood attention/cognitive development) (Figure 5.1). For inclusion in the model, confounding variables had to be associated with birth anthropometric measures and attention problems ( $p < 0.20$ ), or have a strong theoretical basis for inclusion<sup>10</sup>. The successive order of modelling was based on chronology of events affecting the

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<sup>d</sup> OLR yields ordinal odds ratios (ORs), which quantify the likelihood that the exposure (e.g. maternal education level) will cause the value of the outcome (attention or cognitive difficulties) to increase. Positive ORs represent a higher likelihood of impairment.

developing fetus<sup>9</sup> (Table 5.1). This resulted in five models total, with each successive model including all adjustments in previous models.

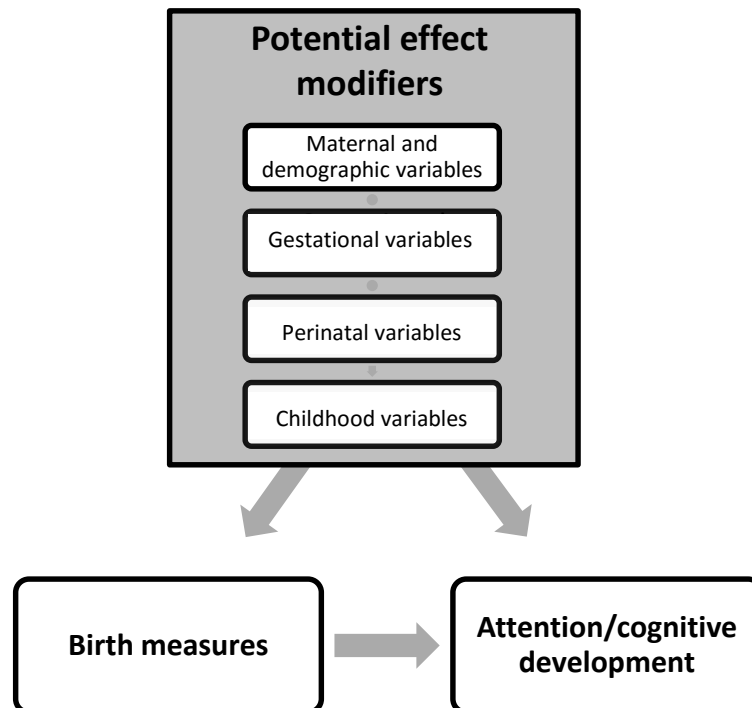


**Figure 5.1. Potential effect modification of confounding variables on association between exposure and outcome**

**Table 5.1. Method of successive adjustment in ordinal logistic regression modelling**

| Model | Variables adjusted for                                                                                                                                                                |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1     | <b>Unadjusted</b>                                                                                                                                                                     |
| 2     | <b>Maternal and demographic variables</b><br>Family income<br>Maternal schooling<br>Maternal age<br>Maternal skin colour<br>Maternal BMI (pre-pregnancy)                              |
| 3     | <b>Gestational variables</b><br>Smoking during pregnancy<br>Alcohol consumption during pregnancy<br>Mental illness during pregnancy<br>High blood pressure during pregnancy<br>Parity |
| 4     | <b>Perinatal variables</b><br>Gestational age at birth<br>Mode of delivery<br>APGAR score at 5 minutes                                                                                |
| 5     | <b>Child nutrition/mother-child morbidity</b><br>Duration of breastfeeding<br>Child hospitalization in first three months<br>Neurological illness in childhood                        |

Each successive model included all adjustments in previous models

7. **Logistic regression modelling (binary outcome):** The modelling analysis was repeated replacing the ordinal outcomes with a dichotomous classification of the attention and cognitive outcomes (clinical and borderline attention/cognitive problems vs no attention/cognitive problems), using logistic regression. Cut-offs for attention problems were a  $t$  score  $\geq 67$  on the CBCL<sup>11</sup>, or a score  $>7$  on the SDQ<sup>12</sup>. For the cognitive domain, cognitive outcomes were cut off at a score  $>1SD$  below cohort mean for the WPPSI-R<sup>7</sup> and the INTER-NDA.
8. **Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and receiver operating characteristics (ROC) analyses:** To compare the ability of birth anthropometric indices to predict attention or cognitive deficits in

childhood, sensitivity<sup>e</sup>, specificity<sup>f</sup>, PPV, NPV<sup>g</sup> and ROC analyses were conducted.

ROC analyses were used to compute the area under the curve (AUC)<sup>h</sup>.

All analyses were performed using IBM SPSS Statistics for Windows 21.0<sup>13</sup>. Further statistical considerations for these analyses are presented in Chapter 3 (Section 3.6).

## 5.3 Results

### 5.3.1 Participants

#### 5.3.1.1 Pelotas

The initial Pelotas sample consisted of 4231 neonates. There were 66 deaths. Data on BW was available for 4228 neonates, birth length (BL) for 4167 neonates, head circumference (HC) for 4170 neonates and gestational age (GA) at delivery for 4217 neonates. At the 48 month follow-up ( $M=49.5$ ,  $SD=1.7$  months), 3799 participants were identified, 3749 completed the CBCL and the WPPSI-R (11.4% loss). There were some differences between the included sample and those lost-to-follow-up in maternal and child characteristics (Table S5.1). The mean BW and BL of the attrition group were significantly lower than those retained in the sample (2978g compared to 3171g and 47.94cm compared to 48.21cm), and the attrition group had more infants born preterm (20.8% compared to 13.8%), with APGAR scores <7 at 5 minutes (6.5% compared to 1.6%). Mothers in the attrition group also had fewer years of schooling (7.8 compared to 8.1 years) and were younger at delivery (25.2 compared to 26.2 years).

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<sup>e</sup> Sensitivity provides a measure of how likely the birth anthropometric indices are to detect the presence of attention or cognitive impairment.

<sup>f</sup> Specificity assesses how likely birth anthropometric indices are to detect the absence of attention or cognitive impairment in children who do not have attention or cognitive difficulties.

<sup>g</sup> PPV and NPV values assess how likely it is that a child with impaired fetal growth will/will not have attention or cognitive impairments.

<sup>h</sup> AUC provides an index of accuracy, assessing the possibility of correctly identifying a randomly selected pair of cases in which one is growth restricted and one is not.

### 5.3.1.2 ALSPAC

The initial ALSPAC sample consisted of 14,062 neonates. There were 74 deaths. Data on BW was available for 13,445 neonates, BL for 10,252 neonates, HC for 10,397 neonates and GA at delivery for 13,616 neonates. The SDQ was assessed in the child-based questionnaire conducted at 81 months ( $M=81.4$ ,  $SD=0.4$  months), with valid data on 7828 children (44.4% loss). The WPPSI-R was conducted on a smaller focus group of 992 children (7.2% of original sample) at 49 months ( $M=48.9$ ,  $SD=0.4$  months). There were some significant differences between the included sample and those lost-to-follow-up in the maternal and child characteristics (Table S5.2). The attrition group had significantly lower mean BW (3375g compared to 3443g), BL (50.54cm compared to 50.76cm) and HC (34.75cm compared to 34.83cm). The attrition group also had a higher prevalence of infants born preterm (5.9% compared to 4.4%) and with APGAR scores  $<7$  (2.1% compared to 1.0%). Mothers in the attrition group had fewer years of schooling (10.33 compared to 11.07 years), were younger at delivery (26.6 compared to 28.9 years) and had a higher prevalence of smoking during pregnancy (32.8% compared to 20.3%).

### 5.3.1.3 INTERGROWTH-21<sup>st</sup>

The total INTERGROWTH-21<sup>st</sup> sample across the UK, Italy, Brazil, India and Kenya sites consisted of 2803 neonates. There were 4 deaths. Of the total sample, 1649 infants were eligible for NDA at the time of data freezing. The INTER-NDA and a subset of the CBCL were conducted at the 24 month follow-up ( $M=24.9$ ,  $SD=2.0$  months), with valid CBCL (attention) data on 1076 children (38.4% of original sample) and INTER-NDA (cognitive) data on 1066 children (65.3% of eligible sample). The only difference between the sample and attrition group was in maternal schooling, with the attrition group having fewer years of schooling than those retained in the sample (14.9 compared to 15.3 years) (Table S5.3).

### 5.3.2 Descriptive statistics and between-group differences

Table 5.2 shows the prevalence of the different birth anthropometric indices across the 3 cohorts. Overall, the Pelotas cohort had the highest prevalence of growth impaired neonates (measured at birth), with more born with low BW, low BL or smaller HC. The ALSPAC cohort had the lowest prevalence of growth impaired neonates at birth, with fewer born with low BW, low BL or low HC. The INTERGROWTH-21<sup>st</sup> cohort was between these two cohorts, with a higher prevalence of growth impairment than ALSPAC, but a lower prevalence than Pelotas (Figure 5.2). Chi-squared analyses showed the frequency distributions significantly differed between cohorts for all indices measured against external references/standards (BW and stunting indices).

**Table 5.2. Prevalence and chi-squared analyses of impaired birth anthropometric indices in the Pelotas, ALSPAC and INTERGROWTH-21st cohorts**

| Variable                                 | Pelotas n (%)<br>(N=3508) | ALSPAC n (%)<br>(N=13445) | INTERGROWTH-21 <sup>st</sup><br>n (%) (N=1076) | $\chi^2$  |
|------------------------------------------|---------------------------|---------------------------|------------------------------------------------|-----------|
| <b>BW indices</b>                        |                           |                           |                                                |           |
| BW <2500g                                | 340 (9.1)                 | 589 (4.4)                 | 73 (6.5)                                       | 127.11**  |
| SGA                                      | 553 (14.8)                | 1154 (8.5)                | 239 (21.3)                                     | 261.65**  |
| BW <10 <sup>th</sup> MGRS                | 694 (18.5)                | 1302 (9.6)                | 202 (17.9)                                     | 256.66**  |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 361 (9.6)                 | 773 (5.7)                 | 135 (12.0)                                     | 115.78**  |
| <b>Stunting indices</b>                  |                           |                           |                                                |           |
| BL < 10 <sup>th</sup> MGRS               | 1057 (28.3)               | 640 (6.2)                 | 156 (13.9)                                     | 1241.86** |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 700 (18.8)                | 413 (4.0)                 | 113 (10.1)                                     | 803.08**  |
| HC <10 <sup>th</sup> MGRS                | 606 (16.2)                | 561 (5.4)                 | 161 (14.4)                                     | 454.24**  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 276 (7.4)                 | 242 (2.3)                 | 80 (7.2)                                       | 220.99**  |
| <b>Wasting indices</b>                   |                           |                           |                                                |           |
| PI <10 <sup>th</sup> percentile          | 374 (10.0)                | 1013 (10.0)               | 111 (9.9)                                      | 0.01      |
| PI-for-age <10 <sup>th</sup> percentile  | 363 (9.7)                 | 1009 (10.0)               | 109 (9.8)                                      | 0.16      |
| BMI <10 <sup>th</sup> percentile         | 372 (10.0)                | 1014 (10.0)               | 111 (9.9)                                      | 0.01      |
| BMI-for-age <10 <sup>th</sup> percentile | 364 (9.8)                 | 1008 (9.9)                | 113 (10.1)                                     | 0.16      |
| <b>Asymmetry indices</b>                 |                           |                           |                                                |           |
| HC/BL >90 <sup>th</sup> percentile       | 370 (9.9)                 | 1024 (9.7)                | 111 (9.9)                                      | 0.02      |
| HC/PI >90 <sup>th</sup> percentile       | 373 (9.9)                 | 1013 (10.0)               | 111 (9.9)                                      | 0.01      |
| HC/BMI >90 <sup>th</sup> percentile      | 373 (9.9)                 | 1012 (10.0)               | 111 (9.9)                                      | 0.01      |

BL=Birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001



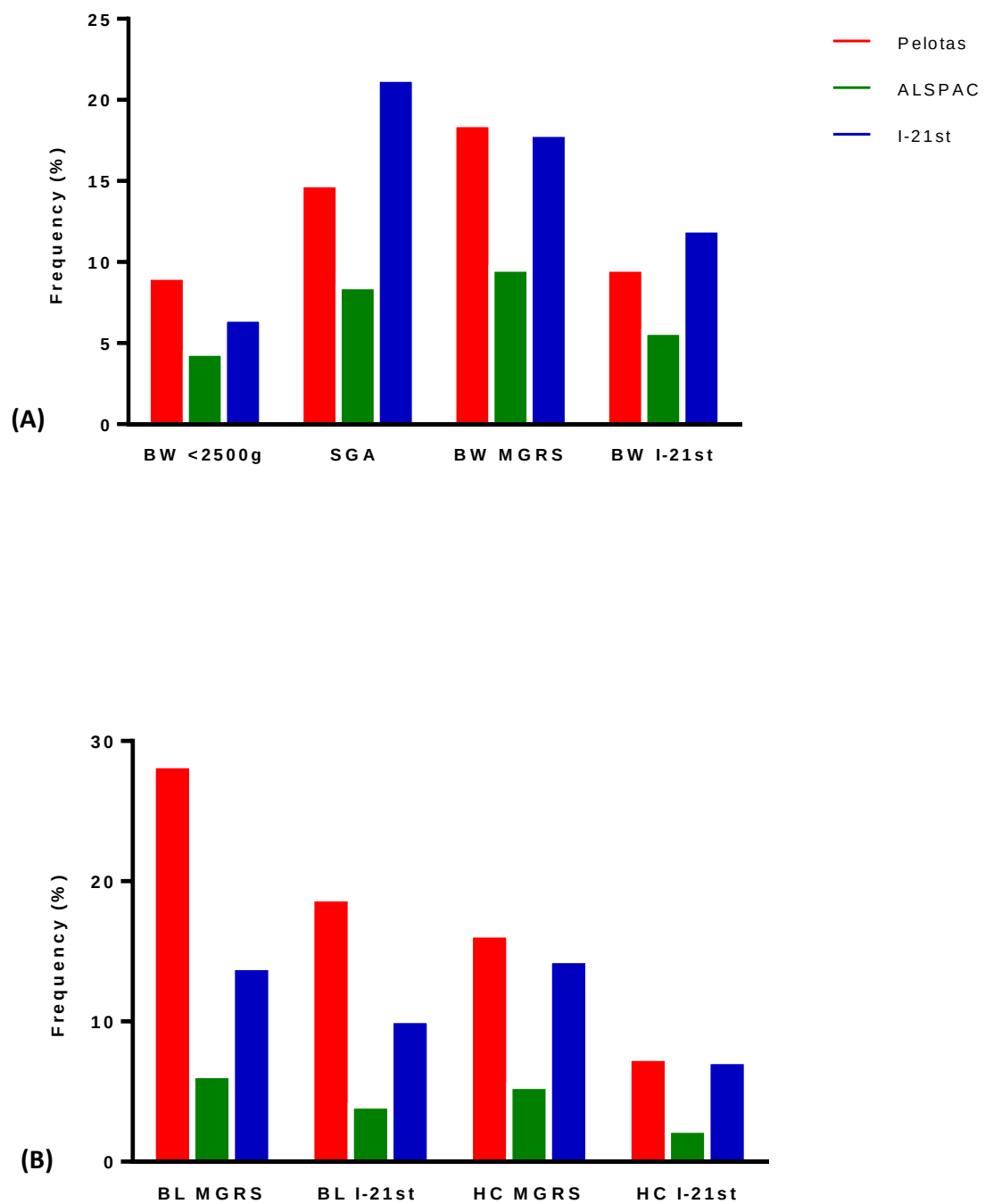


**Figure 5.2. Frequency of (A) BW indices and (B) stunting indices in Pelotas, ALSPAC and INTERGROWTH-21<sup>st</sup>**

Table 5.3 shows the prevalence of poor attention (as measured by the CBCL and SDQ) and cognitive outcomes (as measured by the WPPSI-R and INTER-NDA) across the 3 cohorts. The prevalence of poor attention outcomes ranged from 5.6% to 11.0% and was highest in ALSPAC. The prevalence of poor cognitive outcomes ranged from 16.6% to 21.0% and was highest in INTERGROWTH-21<sup>st</sup> (Figure 5.3). Chi-squared analyses showed the frequency distributions significantly differed between cohorts.

**Table 5.3. Prevalence of cognitive and attention impairments in the Pelotas, ALSPAC and INTERGROWTH-21st cohorts**

| Variable (N) | Pelotas n (%)<br>(N=3749) | ALSPAC n (%)<br>(N=6768) | INTERGROWTH-21 <sup>st</sup><br>n (%) (N=1126) | $\chi^2$ |
|--------------|---------------------------|--------------------------|------------------------------------------------|----------|
| Attention    | 273 (7.3) <sup>a</sup>    | 858 (11.0) <sup>b</sup>  | 60 (5.6) <sup>a</sup>                          | 60.50**  |
| Cognition    | 623 (16.6) <sup>c</sup>   | 154 (17.5) <sup>c</sup>  | 214 (21.0) <sup>d</sup>                        | 86.58**  |

Impairments: <sup>a</sup> = CBCL *t* score  $\geq 67$ ; <sup>b</sup> = SDQ score  $\geq 7$ ; <sup>c</sup> = WPPSI score  $>1SD$  below mean; <sup>d</sup> = INTER-NDA score  $>1SD$  below mean; \* =  $p < .05$ ; \*\* =  $p < .001$

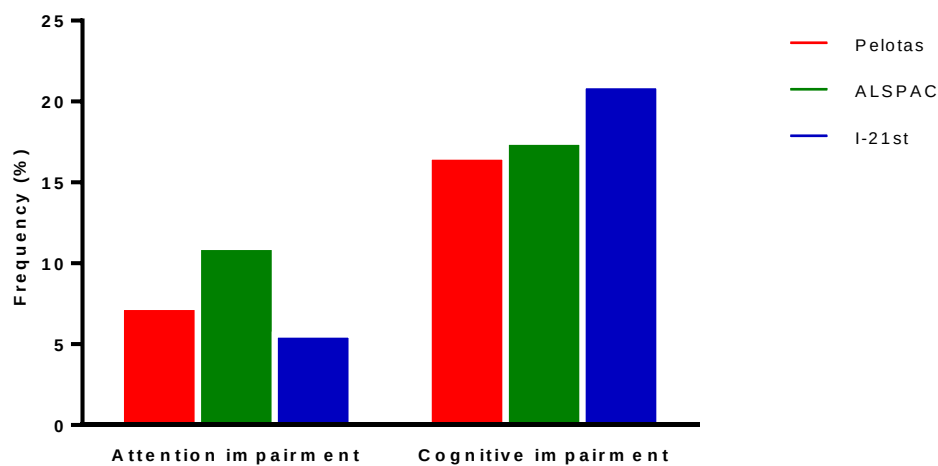


**Figure 5.3. Prevalence of attention and cognitive impairment in Pelotas, ALSPAC and INTERGROWTH-21<sup>st</sup>; Impairments = SDQ score  $\geq 7$ ; CBCL *t* score  $\geq 67$ ; WPPSI score  $>1SD$  below mean; INTER-NDA score  $>1SD$  below mean**

Bivariate correlation coefficients for relationships between the birth anthropometric indices and between attention and cognitive scores are presented in Tables S5.4-S5.6. The direction of all correlations between birth anthropometric indices and between attention and cognitive indices was the same across all three cohorts. Attention and cognitive scores were associated at  $r=-.29$  in both Pelotas and ALSPAC, and  $r=-.35$  in INTERGROWTH-21<sup>st</sup>.

The mean attention and cognitive scores by birth indices for each cohort are presented in Tables S5.7-S5.9. Kruskal-Wallis tests for attention outcomes and between-group univariate ANOVAs for cognitive outcomes, comparing those with LBW, stunting, wasting or asymmetry indices at birth and those with normal growth, are presented in Table 5.4. Equivalent distributions depicted by boxplots and non-statistically significant Levene's tests confirmed that the assumption of homogeneity of variance was upheld. For attention outcomes, Kruskal-Wallis tests showed that in both ALSPAC and Pelotas, children with any of the low BW or stunting indices consistently showed greater attention impairment. The same pattern was found for wasting indices in both the Pelotas and ALSPAC cohorts, although effects were less consistent, and for some asymmetry indices in the Pelotas cohort only. No significant effects were identified for any of the birth indices and attention outcomes in INTERGROWTH-21<sup>st</sup>.

For cognitive outcomes, univariate ANOVA analyses showed that in Pelotas, children with any of the low BW, stunting or wasting indices consistently showed poorer cognitive outcomes. These findings were also identified for the asymmetry indices, although effects were less consistent. In ALSPAC, differences on cognitive scores were identified for two stunting indices (BL <10<sup>th</sup> MGRS and BL <10<sup>th</sup> I-21<sup>st</sup>), but not for BW, wasting or asymmetry indices. There were few effects of birth anthropometric indices identified for cognitive outcomes in the INTERGROWTH-21<sup>st</sup> cohort, with the exception of neonates with BMI <10<sup>th</sup> percentile showing lower cognitive scores in childhood than those with BMI ≥10<sup>th</sup> percentile.

**Table 5.4. Kruskal-Wallis tests ( $\chi^2$ ) of attention outcome and univariate ANOVAs (F) of cognitive outcome scores by birth anthropometric indices**

| Variable                                 | Pelotas   |           | ALSPAC    |           | INTERGROWTH-21st |           |
|------------------------------------------|-----------|-----------|-----------|-----------|------------------|-----------|
|                                          | Attention | Cognition | Attention | Cognition | Attention        | Cognition |
| <b>BW indices</b>                        |           |           |           |           |                  |           |
| BW <2500g                                | 9.55*     | 40.21**   | 13.19**   | 0.63      | 0.12             | 0.19      |
| SGA                                      | 12.29**   | 35.38**   | 14.64**   | 1.40      | 0.03             | 0.14      |
| BW <10 <sup>th</sup> MGRS                | 17.61**   | 57.17**   | 23.08**   | 3.01      | 1.91             | 0.10      |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 17.46**   | 35.36**   | 17.43**   | 1.39      | 0.00             | 0.83      |
| <b>Stunting indices</b>                  |           |           |           |           |                  |           |
| BL < 10 <sup>th</sup> MGRS               | 20.31**   | 49.50**   | 13.55**   | 3.96*     | 0.23             | 2.07      |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 18.83**   | 34.63**   | 15.66**   | 4.64*     | 1.08             | 0.02      |
| HC <10 <sup>th</sup> MGRS                | 29.04**   | 90.63**   | 20.65**   | 3.63      | 2.32             | 0.86      |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 11.20*    | 55.07**   | 5.67*     | 4.22*     | 0.41             | 0.67      |
| <b>Wasting indices</b>                   |           |           |           |           |                  |           |
| PI <10 <sup>th</sup> percentile          | 5.37*     | 27.68**   | 2.69      | 0.56      | 1.48             | 2.86      |
| PI-for-age <10 <sup>th</sup> percentile  | 0.72      | 6.10*     | 0.54      | 0.11      | 2.90             | 3.52      |
| BMI <10 <sup>th</sup> percentile         | 11.17*    | 51.88**   | 5.06*     | 0.12      | 2.80             | 6.01*     |
| BMI-for-age <10 <sup>th</sup> percentile | 6.04*     | 12.86**   | 4.97*     | 0.04      | 1.52             | 2.22      |
| <b>Asymmetry indices</b>                 |           |           |           |           |                  |           |
| HC/BL >90 <sup>th</sup> percentile       | 6.72*     | 7.99*     | 2.61      | 0.09      | 0.96             | 0.16      |
| HC/PI >90 <sup>th</sup> percentile       | 0.12      | 0.55      | 0.06      | 0.31      | 0.05             | 2.63      |
| HC/BMI >90 <sup>th</sup> percentile      | 4.37*     | 24.29**   | 3.36      | 0.57      | 0.03             | 1.35      |

BL=BIRTH LENGTH; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

### **5.3.3 Association between confounding variables and attention and cognitive impairment**

The effect of potential confounders on attention and cognitive outcomes were examined using univariable OLR analyses.

#### **5.3.3.1 Pelotas**

In the Pelotas cohort, poorer attention and cognitive outcomes were associated with a number of maternal, demographic and gestational variables (Table S5.10). Specifically, poorer attention and cognitive outcomes were associated with lower family income, lower maternal schooling, lower maternal age at birth, black/other maternal skin colour, parity (siblings provided a protective effect), smoking during pregnancy, maternal mental illness during pregnancy and high blood pressure during pregnancy. There were a number of perinatal and childhood factors that also increased the likelihood of poor attention and cognitive outcomes (Table S5.11). These included male sex, lower GA at birth, low APGAR score at 5 minutes, breastfeeding  $\geq 6$  months in duration, hospitalisation during the first 3 months of life, presence of neurological illness during childhood, and a small HC, and low height-for-age at two years of age. Caesarean section was found to be protective for poor attention and cognitive outcomes, indicative of the higher level of education and income associated with caesarean section in this cohort.

#### **5.3.3.2 ALSPAC**

In ALSPAC, poorer attention and cognitive outcomes were associated with a number of maternal, demographic and gestational factors (Table S5.12). These included lower family income, lower maternal schooling, lower maternal age at birth, parity (siblings provided a protective effect against attention impairment), smoking during pregnancy, and maternal mental illness during pregnancy. There were shown to be a number of perinatal and childhood

factors that increased the likelihood of poor attention and cognitive outcomes (Table S5.13). These included male sex, preterm delivery, and less than six months of breastfeeding.

### 5.3.3.3 INTERGROWTH-21<sup>st</sup>

In INTERGROWTH-21<sup>st</sup>, there were fewer associations between poorer attention and cognitive outcomes and maternal, demographic gestational, perinatal and childhood factors (Table S5.14). Lower maternal age and higher rates of caesarean section were associated with poorer attention outcomes, and male sex was associated with poorer cognitive outcomes. Table 5.5 provides a summary of some of the significant associations between confounding variables and attention and cognitive outcomes across the three cohorts.

**Table 5.5. Significant associations between maternal and child characteristics, and poorer attention and cognitive outcomes in Pelotas, ALSPAC and INTERGROWTH-21<sup>st</sup>**

| Variable (N)                   | Attention |        |                                 | Cognition |        |                                 |
|--------------------------------|-----------|--------|---------------------------------|-----------|--------|---------------------------------|
|                                | Pelotas   | ALSPAC | I-21 <sup>st</sup> <sup>i</sup> | Pelotas   | ALSPAC | I-21 <sup>st</sup> <sup>i</sup> |
| Low family income              | +         | +      | n/a                             | +         | +      | n/a                             |
| Low maternal schooling (years) | +         | +      | -                               | +         | +      | -                               |
| Low maternal age (years)       | +         | +      | +                               | +         | +      | +                               |
| Low maternal BMI               | +         | +      | -                               | -         | -      | -                               |
| Smoked during pregnancy        | +         | +      | n/a                             | +         | +      | n/a                             |
| Diabetes during pregnancy      | +         | +      | n/a                             | -         | -      | n/a                             |
| Sex of child (male)            | +         | +      | +                               | +         | +      | +                               |
| Low GA at birth                | +         | +      | +                               | +         | +      | +                               |
| Mode of delivery (cesarean)    | - *       | -      | +                               | - **      | +      | +                               |
| Low APGAR score at 5 min       | +         | - *    | +                               | +         | -      | -                               |
| Breastfeeding (<6 months)      | +         | +      | -                               | +         | +      | +                               |

<sup>i</sup> "Low" in I-21<sup>st</sup> is relative to others rather than objective, given I-21<sup>st</sup> is a low risk sample; + = OR > 1.00 (positive association); - = OR < 1.00 (negative association); n/a = data not available; \* = p < .05; \*\* = p < .001

#### **5.3.4 Association between birth anthropometric indices and attention and cognitive outcomes**

To assess the unadjusted associations between birth anthropometric indices and attention and cognitive outcomes, and to assess the effect of adjustment for confounding variables, univariable and multivariable OLR analyses were conducted in five successive models. First, modelling was conducted unadjusted, then successively adjusted for maternal/demographic variables, gestational variables, perinatal variables and childhood/nutrition variables.

##### **5.3.4.1 Association between birth anthropometric indices and attention outcomes**

In Pelotas, unadjusted models showed associations with most birth anthropometric indices and poorer attention outcomes in childhood (with the exception of PI-for-age and HC/PI) (Table 5.6). After adjustment for maternal, demographic and gestational variables, all statistically significant associations for BW and stunting indices remained, however only associations with one wasting index (BMI<10<sup>th</sup> percentile) and one asymmetry index (HC/PL >90<sup>th</sup> percentile) remained (Table S5.15). Following full adjustment (also including perinatal and childhood variables), associations remained between three BW indices (SGA, BW<10<sup>th</sup> MGRS and BW<10<sup>th</sup> I-21<sup>st</sup>) and three stunting indices (BL<10<sup>th</sup> MGRS, BL<10<sup>th</sup> I-21<sup>st</sup> and HC<10<sup>th</sup> MGRS). No significant associations remained between any of the wasting or asymmetry indices and childhood attention.

**Table 5.6. Unadjusted and adjusted associations between birth anthropometric indices and higher attention score in childhood in Pelotas**

| Variables                                | Unadjusted |           |         | Fully adjusted |           |       |
|------------------------------------------|------------|-----------|---------|----------------|-----------|-------|
|                                          | OR         | 95%CI     | p       | OR             | 95%CI     | p     |
| <b>BW indices</b>                        |            |           |         |                |           |       |
| BW <2500g                                | 1.38       | 1.13-1.68 | .002*   | 1.15           | 0.90-1.47 | .255  |
| SGA                                      | 1.33       | 1.14-1.56 | <.001** | 1.23           | 1.04-1.47 | .017* |
| BW <10 <sup>th</sup> MGRS                | 1.37       | 1.18-1.58 | <.001** | 1.21           | 1.02-1.44 | .033* |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.53       | 1.26-1.86 | <.001** | 1.38           | 1.12-1.70 | .003* |
| <b>Stunting indices</b>                  |            |           |         |                |           |       |
| BL <10 <sup>th</sup> MGRS                | 1.34       | 1.18-1.52 | <.001** | 1.20           | 1.04-1.39 | .015* |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.38       | 1.19-1.59 | <.001** | 1.24           | 1.06-1.46 | .009* |
| HC <10 <sup>th</sup> MGRS                | 1.52       | 1.31-1.78 | <.001** | 1.37           | 1.14-1.64 | .001* |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.44       | 1.16-1.78 | .001*   | 1.26           | 1.00-1.58 | .053  |
| <b>Wasting indices</b>                   |            |           |         |                |           |       |
| PI <10 <sup>th</sup> percentile          | 1.25       | 1.04-1.51 | .020*   | 1.15           | 0.94-1.41 | .189  |
| PI-for-age <10 <sup>th</sup> percentile  | 1.09       | 0.90-1.31 | .397    | 1.06           | 0.86-1.29 | .603  |
| BMI <10 <sup>th</sup> percentile         | 1.39       | 1.15-1.68 | .001*   | 1.19           | 0.96-1.48 | .122  |
| BMI-for-age <10 <sup>th</sup> percentile | 1.27       | 1.05-1.54 | .013*   | 1.21           | 0.99-1.49 | .063  |
| <b>Asymmetry indices</b>                 |            |           |         |                |           |       |
| HC/BL >90 <sup>th</sup> percentile       | 1.29       | 1.06-1.55 | .009*   | 1.19           | 0.97-1.46 | .088  |
| HC/PI >90 <sup>th</sup> percentile       | 1.03       | 0.86-1.25 | .729    | 1.04           | 0.85-1.27 | .711  |
| HC/BMI >90 <sup>th</sup> percentile      | 1.22       | 1.01-1.47 | .037*   | 1.15           | 0.93-1.41 | .193  |

Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=Birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001



In ALSPAC, unadjusted models revealed associations between all BW and stunting indices, and two wasting indices (BMI<10<sup>th</sup> percentile and BMI-for-age <10<sup>th</sup> percentile) and poorer attention outcomes (Table 5.7). After adjustment for maternal, demographic and gestational variables, statistically significant associations remained for three BW indices (BW<2500g, SGA and BW<10<sup>th</sup> MGRS) and two stunting indices (BL<10<sup>th</sup> MGRS and HC<10<sup>th</sup> MGRS) (Table S5.16). Following full adjustment, associations remained between BW indices (SGA and BW<10<sup>th</sup> MGRS), and one stunting index (BL<10<sup>th</sup> MGRS) and poorer attention outcomes. There were no statistically significant associations with any wasting or asymmetry indices.

**Table 5.7. Unadjusted and adjusted associations between birth anthropometric indices and higher attention score in childhood in ALSPAC**

| Variables                                | Unadjusted |           |         | Fully adjusted |           |       |
|------------------------------------------|------------|-----------|---------|----------------|-----------|-------|
|                                          | OR         | 95%CI     | p       | OR             | 95%CI     | p     |
| <b>BW indices</b>                        |            |           |         |                |           |       |
| BW <2500g                                | 1.49       | 1.21-1.82 | <.001** | 2.12           | 0.82-0.49 | .122  |
| SGA                                      | 1.35       | 1.17-1.56 | <.001** | 1.84           | 1.01-3.34 | .046* |
| BW <10 <sup>th</sup> MGRS                | 1.41       | 1.23-1.63 | <.001** | 2.11           | 1.13-3.95 | .020* |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.45       | 1.22-1.73 | <.001** | 1.41           | 0.69-2.85 | .346  |
| <b>Stunting indices</b>                  |            |           |         |                |           |       |
| BL < 10 <sup>th</sup> MGRS               | 1.43       | 1.18-1.73 | <.001** | 2.84           | 1.42-5.69 | .003* |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.60       | 1.27-2.02 | <.001** | 2.13           | 0.90-5.03 | .085  |
| HC <10 <sup>th</sup> MGRS                | 1.59       | 1.31-1.94 | <.001** | 1.94           | 0.78-4.81 | .155  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.36       | 1.03-1.80 | .033*   | 0.75           | 0.26-2.16 | .595  |
| <b>Wasting indices</b>                   |            |           |         |                |           |       |
| PI <10 <sup>th</sup> percentile          | 1.13       | 0.98-1.31 | .103    | 1.03           | 0.59-1.78 | .925  |
| PI-for-age <10 <sup>th</sup> percentile  | 1.06       | 0.91-1.22 | .468    | 1.15           | 0.68-1.96 | .602  |
| BMI <10 <sup>th</sup> percentile         | 1.19       | 1.02-1.38 | .025*   | 1.62           | 0.93-2.84 | .088  |
| BMI-for-age <10 <sup>th</sup> percentile | 1.19       | 1.02-1.38 | .025*   | 1.29           | 0.75-2.21 | .361  |
| <b>Asymmetry indices</b>                 |            |           |         |                |           |       |
| HC/BL >90 <sup>th</sup> percentile       | 1.13       | 0.97-1.31 | .107    | 1.54           | 0.87-2.74 | .142  |
| HC/PI >90 <sup>th</sup> percentile       | 0.98       | 0.85-1.14 | .811    | 1.06           | 0.61-1.85 | .828  |
| HC/BMI >90 <sup>th</sup> percentile      | 1.15       | 0.99-1.33 | .068    | 1.57           | 0.89-2.78 | .120  |

Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=Birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

In INTERGROWTH-21<sup>st</sup>, unadjusted models revealed no statistically significant associations between any of the birth anthropometric indices and poorer attention outcomes (Table 5.8). After adjustment for maternal, demographic, gestational and perinatal variables, BW<2500g was significantly associated with poorer attention outcomes (Table S5.17), however after full adjustment this association became non-significant.

**Table 5.8. Unadjusted and adjusted associations between birth anthropometric indices and higher attention score in childhood in INTERGROWTH-21st**

| Variables                                | Unadjusted |           |          | Fully adjusted |           |          |
|------------------------------------------|------------|-----------|----------|----------------|-----------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI     | <i>p</i> |
| <b>BW indices</b>                        |            |           |          |                |           |          |
| BW <2500g                                | 0.91       | 0.59-1.43 | .691     | 0.61           | 0.37-1.01 | .053     |
| SGA                                      | 1.01       | 0.78-1.31 | .930     | 0.90           | 0.69-1.18 | .440     |
| BW <10 <sup>th</sup> MGRS                | 1.21       | 0.92-1.61 | .179     | 0.96           | 0.70-1.33 | .822     |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.98       | 0.71-1.37 | .912     | 0.87           | 0.62-1.22 | .423     |
| <b>Stunting indices</b>                  |            |           |          |                |           |          |
| BL <10 <sup>th</sup> MGRS                | 1.09       | 0.80-1.49 | .587     | 0.87           | 0.62-1.23 | .429     |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.22       | 0.84-1.77 | .290     | 1.25           | 0.86-1.82 | .251     |
| HC <10 <sup>th</sup> MGRS                | 1.26       | 0.93-1.72 | .136     | 0.95           | 0.67-1.34 | .760     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.14       | 0.74-1.75 | .550     | 0.97           | 0.63-1.50 | .893     |
| <b>Wasting indices</b>                   |            |           |          |                |           |          |
| PI <10 <sup>th</sup> percentile          | 1.23       | 0.86-1.76 | .251     | 0.99           | 0.68-1.44 | .967     |
| PI-for-age <10 <sup>th</sup> percentile  | 1.36       | 0.95-1.96 | .097     | 1.18           | 0.82-1.71 | .378     |
| BMI <10 <sup>th</sup> percentile         | 1.34       | 0.94-1.90 | .108     | 1.00           | 0.68-1.48 | .987     |
| BMI-for-age <10 <sup>th</sup> percentile | 1.23       | 0.87-1.75 | .246     | 1.07           | 0.75-1.54 | .692     |
| <b>Asymmetry indices</b>                 |            |           |          |                |           |          |
| HC/BL >90 <sup>th</sup> percentile       | 0.85       | 0.60-1.21 | .367     | 0.87           | 0.60-1.26 | .466     |
| HC/PI >90 <sup>th</sup> percentile       | 1.03       | 0.72-1.47 | .894     | 0.88           | 0.61-1.27 | .497     |
| HC/BMI >90 <sup>th</sup> percentile      | 1.02       | 0.71-1.46 | .921     | 0.81           | 0.56-1.18 | .271     |

Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=Birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* =  $p < .05$ ; \*\*= $p < .001$

A summary table of the direction and significance of unadjusted and adjusted associations for attention outcomes across all three cohorts is presented in Table 5.9.

**Table 5.9. Significant associations between indices of fetal growth impairment and higher attention scores in Pelotas, ALSPAC and INTERGROWTH-21st**

| Variable                                 | Unadjusted |        |        | Adjusted |        |        |
|------------------------------------------|------------|--------|--------|----------|--------|--------|
|                                          | Pelotas    | ALSPAC | I-21st | Pelotas  | ALSPAC | I-21st |
| <b>BW indices</b>                        |            |        |        |          |        |        |
| BW <2500g                                | +          | +      | -      | +        | +      | -      |
| SGA                                      | +          | +      | +      | +        | +      | -      |
| BW <10 <sup>th</sup> MGRS                | +          | +      | +      | +        | +      | -      |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | +          | +      | -      | +        | +      | -      |
| <b>Stunting indices</b>                  |            |        |        |          |        |        |
| BL <10 <sup>th</sup> MGRS                | +          | +      | +      | +        | +      | -      |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | +          | +      | +      | +        | +      | +      |
| HC <10 <sup>th</sup> MGRS                | +          | +      | +      | +        | +      | -      |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | +          | +      | +      | +        | -      | -      |
| <b>Wasting indices</b>                   |            |        |        |          |        |        |
| PI <10 <sup>th</sup> percentile          | +          | +      | +      | +        | +      | -      |
| PI-for-age <10 <sup>th</sup> percentile  | +          | +      | +      | +        | +      | +      |
| BMI <10 <sup>th</sup> percentile         | +          | +      | +      | +        | +      | +      |
| BMI-for-age <10 <sup>th</sup> percentile | +          | +      | +      | +        | +      | +      |
| <b>Asymmetry indices</b>                 |            |        |        |          |        |        |
| HC/BL >90 <sup>th</sup> percentile       | +          | +      | -      | +        | +      | -      |
| HC/PI >90 <sup>th</sup> percentile       | +          | -      | +      | +        | +      | -      |
| HC/BMI >90 <sup>th</sup> percentile      | +          | +      | +      | +        | +      | -      |

+ = OR > 1.00 (positive association); - = OR < 1.00 (negative association); \* = p < .05; \*\* = p < .001

#### **5.3.4.2 Association between birth anthropometric indices and cognitive outcomes**

In Pelotas, unadjusted models showed a statistically significant association between all of the birth anthropometric indices and poorer cognitive outcomes, with the exception of HC/PI >90<sup>th</sup> percentile (Table 5.10). Following adjustment for maternal, demographic, gestational and perinatal variables, all associations remained, with the exception of PI-for-age <10<sup>th</sup> percentile (Table S5.18). Following full adjustment (further adjusting for childhood variables), associations remained between all BW indices (with the exception of BW<2500g), all stunting indices, two wasting indices (PI <10<sup>th</sup> percentile and BMI <10<sup>th</sup> percentile) and one asymmetry index (HC/BMI >90<sup>th</sup> percentile) and poorer cognitive outcomes.

**Table 5.10. Unadjusted and adjusted associations between birth anthropometric indices and lower cognitive scores in childhood in Pelotas**

| Variables                                | Unadjusted |           |         | Fully adjusted |           |         |
|------------------------------------------|------------|-----------|---------|----------------|-----------|---------|
|                                          | OR         | 95%CI     | p       | OR             | 95%CI     | p       |
| <b>BW indices</b>                        |            |           |         |                |           |         |
| BW <2500g                                | 1.85       | 1.51-2.27 | <.001** | 1.21           | 0.94-1.55 | .138    |
| SGA                                      | 1.57       | 1.34-1.86 | <.001** | 1.27           | 1.07-1.52 | .008*   |
| BW <10 <sup>th</sup> MGRS                | 1.71       | 1.47-1.98 | <.001** | 1.20           | 1.00-1.44 | .047*   |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.74       | 1.43-2.12 | <.001** | 1.34           | 1.08-1.67 | .008*   |
| <b>Stunting indices</b>                  |            |           |         |                |           |         |
| BL < 10 <sup>th</sup> MGRS               | 1.57       | 1.38-1.79 | <.001** | 1.18           | 1.02-1.38 | .032*   |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.56       | 1.34-1.81 | <.001** | 1.30           | 1.10-1.54 | .002*   |
| HC <10 <sup>th</sup> MGRS                | 2.02       | 1.72-2.38 | <.001** | 1.42           | 1.17-1.71 | <.001** |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.15       | 1.72-2.69 | <.001** | 1.53           | 1.20-1.95 | .001*   |
| <b>Wasting indices</b>                   |            |           |         |                |           |         |
| PI <10 <sup>th</sup> percentile          | 1.60       | 1.32-1.94 | <.001** | 1.33           | 1.08-1.64 | .008*   |
| PI-for-age <10 <sup>th</sup> percentile  | 1.24       | 1.02-1.51 | .031*   | 1.12           | 0.91-1.39 | .284    |
| BMI <10 <sup>th</sup> percentile         | 1.93       | 1.59-2.36 | <.001** | 1.37           | 1.09-1.72 | .006*   |
| BMI-for-age <10 <sup>th</sup> percentile | 1.35       | 1.11-1.64 | .003*   | 1.15           | 0.93-1.42 | .202    |
| <b>Asymmetry indices</b>                 |            |           |         |                |           |         |
| HC/BL >90 <sup>th</sup> percentile       | 1.27       | 1.04-1.54 | .018*   | 1.20           | 0.97-1.49 | .101    |
| HC/PI >90 <sup>th</sup> percentile       | 1.06       | 0.88-1.28 | .548    | 1.10           | 0.89-1.35 | .387    |
| HC/BMI >90 <sup>th</sup> percentile      | 1.55       | 1.28-1.89 | <.001** | 1.34           | 1.08-1.67 | .008*   |

Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=Birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

In ALSPAC, unadjusted models revealed no statistically significant associations between any of the birth anthropometric indices and poorer cognitive outcomes (Table 5.11). After adjustment for maternal, demographic, gestational and perinatal variables, one BW index (BW <10<sup>th</sup> MGRS) and one stunting index (BL <10<sup>th</sup> MGRS) were associated with poorer cognitive scores (Table S5.19). Following full adjustment, however, only BW <10<sup>th</sup> MGRS remained significantly associated with poorer cognitive outcomes.



**Table 5.11. Unadjusted and adjusted associations between birth anthropometric indices and lower cognitive scores in childhood in ALSPAC**

| Variables                                | Unadjusted |           |      | Fully adjusted |           |       |
|------------------------------------------|------------|-----------|------|----------------|-----------|-------|
|                                          | OR         | 95%CI     | p    | OR             | 95%CI     | p     |
| <b>BW indices</b>                        |            |           |      |                |           |       |
| BW <2500g                                | 1.14       | 0.60-2.15 | .689 | 2.22           | 0.51-9.71 | .288  |
| SGA                                      | 1.17       | 0.75-1.81 | .493 | 0.86           | 0.33-2.25 | .752  |
| BW <10 <sup>th</sup> MGRS                | 1.39       | 0.91-2.12 | .125 | 2.48           | 1.30-4.73 | .006* |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.38       | 0.80-2.37 | .239 | 1.50           | 0.42-5.39 | .539  |
| <b>Stunting indices</b>                  |            |           |      |                |           |       |
| BL <10 <sup>th</sup> MGRS                | 1.40       | 0.84-2.34 | .200 | 1.77           | 0.86-3.64 | .121  |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.72       | 0.87-3.41 | .122 | 1.60           | 0.58-4.46 | .368  |
| HC <10 <sup>th</sup> MGRS                | 1.43       | 0.81-2.52 | .214 | 1.12           | 0.30-4.22 | .869  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.03       | 0.93-4.45 | .076 | 1.10           | 0.25-4.90 | .899  |
| <b>Wasting indices</b>                   |            |           |      |                |           |       |
| PI <10 <sup>th</sup> percentile          | 1.09       | 0.76-1.55 | .641 | 0.94           | 0.53-1.66 | .822  |
| PI-for-age <10 <sup>th</sup> percentile  | 0.99       | 0.69-1.42 | .959 | 0.93           | 0.52-1.65 | .812  |
| BMI <10 <sup>th</sup> percentile         | 1.03       | 0.72-1.49 | .859 | 1.22           | 0.70-2.16 | .483  |
| BMI-for-age <10 <sup>th</sup> percentile | 0.95       | 0.64-1.39 | .772 | 1.06           | 0.60-1.86 | .840  |
| <b>Asymmetry indices</b>                 |            |           |      |                |           |       |
| HC/BL >90 <sup>th</sup> percentile       | 0.98       | 0.61-1.57 | .936 | 1.01           | 0.54-1.90 | .979  |
| HC/PI >90 <sup>th</sup> percentile       | 1.00       | 0.67-1.44 | .994 | 1.04           | 0.61-1.80 | .876  |
| HC/BMI >90 <sup>th</sup> percentile      | 1.00       | 0.71-1.49 | .872 | 1.01           | 0.56-1.81 | .974  |

Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=Birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

In INTERGROWTH-21<sup>st</sup>, unadjusted models revealed no statistically significant associations between any of the birth anthropometric indices and poorer cognitive outcomes (Table 5.12). After adjustment for maternal, demographic, gestational and perinatal variables, one stunting index, BL <10<sup>th</sup> MGRS (Table S5.20) was found to be significantly associated with poorer cognitive outcomes, however this did not withstand full adjustment (including childhood variables).

**Table 5.12. Unadjusted and adjusted associations between birth anthropometric indices and lower cognitive score in childhood in INTERGROWTH-21st**

| Variables                                | Unadjusted |           |      | Fully adjusted |           |      |
|------------------------------------------|------------|-----------|------|----------------|-----------|------|
|                                          | OR         | 95%CI     | p    | OR             | 95%CI     | p    |
| <b>BW indices</b>                        |            |           |      |                |           |      |
| BW <2500g                                | 0.79       | 0.49-1.26 | .320 | 0.70           | 0.41-1.20 | .194 |
| SGA                                      | 0.92       | 0.70-1.21 | .542 | 0.90           | 0.67-1.21 | .488 |
| BW <10 <sup>th</sup> MGRS                | 0.92       | 0.68-1.24 | .574 | 0.88           | 0.62-1.25 | .474 |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.09       | 0.78-1.54 | .611 | 1.07           | 0.75-1.53 | .720 |
| <b>Stunting indices</b>                  |            |           |      |                |           |      |
| BL <10 <sup>th</sup> MGRS                | 0.75       | 0.54-1.04 | .080 | 0.68           | 0.41-1.13 | .133 |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.93       | 0.64-1.34 | .686 | 0.89           | 0.61-1.34 | .563 |
| HC <10 <sup>th</sup> MGRS                | 1.04       | 0.75-1.46 | .797 | 1.00           | 0.68-1.46 | .985 |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.07       | 0.68-1.68 | .782 | 1.03           | 0.65-1.65 | .890 |
| <b>Wasting indices</b>                   |            |           |      |                |           |      |
| PI <10 <sup>th</sup> percentile          | 1.33       | 0.90-1.96 | .153 | 1.31           | 0.87-1.97 | .200 |
| PI-for-age <10 <sup>th</sup> percentile  | 1.44       | 0.98-2.10 | .061 | 1.42           | 0.95-2.10 | .086 |
| BMI <10 <sup>th</sup> percentile         | 1.44       | 0.99-2.11 | .059 | 1.43           | 0.94-2.20 | .098 |
| BMI-for-age <10 <sup>th</sup> percentile | 1.23       | 0.85-1.78 | .265 | 1.18           | 0.80-1.74 | .397 |
| <b>Asymmetry indices</b>                 |            |           |      |                |           |      |
| HC/BL >90 <sup>th</sup> percentile       | 0.94       | 0.65-1.36 | .736 | 0.88           | 0.60-1.29 | .503 |
| HC/PI >90 <sup>th</sup> percentile       | 1.38       | 0.95-2.02 | .094 | 1.33           | 0.90-1.98 | .159 |
| HC/BMI >90 <sup>th</sup> percentile      | 1.10       | 0.74-1.63 | .637 | 1.07           | 0.71-1.62 | .754 |

Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=Birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

A summary table of the direction and significance of unadjusted and adjusted associations for cognitive outcomes across all three cohorts is presented in Table 5.13.

**Table 5.13. Significant associations between indices of fetal growth impairment and lower cognitive scores in Pelotas, ALSPAC and INTERGROWTH-21st**

| Variable (N)                             | Unadjusted |        |        | Adjusted |        |        |
|------------------------------------------|------------|--------|--------|----------|--------|--------|
|                                          | Pelotas    | ALSPAC | I-21st | Pelotas  | ALSPAC | I-21st |
| <b>BW indices</b>                        |            |        |        |          |        |        |
| BW <2500g                                | ***        | +      | -      | +        | +      | -      |
| SGA                                      | ***        | +      | -      | +        | -      | -      |
| BW <10 <sup>th</sup> MGRS                | ***        | +      | -      | +        | -      | -      |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | ***        | +      | +      | +        | +      | +      |
| <b>Stunting indices</b>                  |            |        |        |          |        |        |
| BL <10 <sup>th</sup> MGRS                | ***        | +      | -      | +        | +      | -      |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | ***        | +      | -      | +        | +      | -      |
| HC <10 <sup>th</sup> MGRS                | ***        | +      | +      | ***      | +      | +      |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | ***        | +      | +      | +        | +      | +      |
| <b>Wasting indices</b>                   |            |        |        |          |        |        |
| PI <10 <sup>th</sup> percentile          | ***        | +      | +      | +        | -      | +      |
| PI-for-age <10 <sup>th</sup> percentile  | +          | -      | +      | +        | -      | +      |
| BMI <10 <sup>th</sup> percentile         | ***        | +      | +      | +        | +      | +      |
| BMI-for-age <10 <sup>th</sup> percentile | +          | -      | +      | +        | +      | +      |
| <b>Asymmetry indices</b>                 |            |        |        |          |        |        |
| HC/BL >90 <sup>th</sup> percentile       | +          | -      | -      | +        | +      | -      |
| HC/PI >90 <sup>th</sup> percentile       | +          | +      | +      | +        | +      | +      |
| HC/BMI >90 <sup>th</sup> percentile      | ***        | +      | +      | +        | +      | +      |

+ = OR > 1.00 (positive association); - = OR < 1.00 (negative association); \* = p < .05; \*\* = p < .001

### 5.3.4.3 Association between birth anthropometric indices and clinical-level attention and cognitive impairment

To examine the associations between birth anthropometric indices and dichotomous attention and cognitive outcomes (clinical and borderline attention and mild cognitive impairment vs normal), the unadjusted and fully adjusted analyses were repeated comparing those with clinical and borderline attention and cognitive problems to no attention or cognitive problems. Clinical or borderline attention problems were identified in 7.3% of the Pelotas sample, 11.0% of the ALSPAC sample and 5.6% of the INTERGROWTH-21<sup>st</sup> sample. Mild cognitive impairment (>1SD below cohort mean) was identified in 16.6% of the Pelotas sample, 17.5% of the ALSPAC sample and 21.0% of the INTERGROWTH-21<sup>st</sup> sample (Table 5.3).

The results of the dichotomous analyses were in support of those obtained using the ordinal attention and cognitive outcomes. For attention outcomes, following full adjustment, BW and stunting indices were associated with attention impairment in Pelotas (SGA, BW <10<sup>th</sup> MGRS, BW <10<sup>th</sup> I-21<sup>st</sup>, and BL <10<sup>th</sup> I-21<sup>st</sup>) and ALSPAC (SGA, BW <10<sup>th</sup> MGRS, and BL <10<sup>th</sup> MGRS), however there were no statistically significant associations identified in INTERGROWTH-21<sup>st</sup> (Tables S5.21-S5.23).

For cognitive outcomes, following full adjustment, BW (BW <10<sup>th</sup> I-21<sup>st</sup>), stunting (BL <10<sup>th</sup> I-21<sup>st</sup>, HC <10<sup>th</sup> MGRS, and HC <10<sup>th</sup> I-21<sup>st</sup>), and asymmetry (HC/BMI >90<sup>th</sup> percentile) were associated with cognitive impairment in Pelotas. Interestingly, no wasting indices were found to be associated with cognitive impairment in Pelotas using dichotomous outcomes. No statistically significant associations were identified in ALSPAC or INTERGROWTH-21<sup>st</sup> for dichotomous outcomes following full adjustment (Tables S5.24-S5.26).

### 5.3.5 Sensitivity, specificity and receiver-operating characteristic (ROC) analysis

Sensitivity, specificity, PPV, NPV and AUC for each of the birth anthropometric indices were assessed to compare the indices on predictive value. All indices were shown to have lower sensitivity and PPV, and higher specificity and NPV.

For attention outcomes, in Pelotas, BW and stunting indices were better predictors across all four measures (sensitivity, specificity, PPV and NPV) than wasting or asymmetry indices. The strongest BW index was  $BW < 10^{\text{th}}$  I-21<sup>st</sup> and the strongest stunting index was  $BL < 10^{\text{th}}$  I-21<sup>st</sup> (Table 5.14). The sensitivity for  $BL < 10^{\text{th}}$  I-21<sup>st</sup> was 27.0%. This means that of all children with attention impairment on the CBCL, 27.0% had a  $BL < 10^{\text{th}}$  percentile according to INTERGROWTH-21<sup>st</sup> standards. There were 273 children with attention impairment in Pelotas, therefore 73 of them had a  $BL < 10^{\text{th}}$  percentile according to INTERGROWTH-21<sup>st</sup> standards (200 children with attention impairment were in the normal range for BL). The specificity was 81.9%. This means that of all children who scored in the normal range of the CBCL, 81.9% had  $BL \geq 10^{\text{th}}$  percentile according to INTERGROWTH-21<sup>st</sup> standards. There were 3476 children who scored in the normal range, therefore 2,846 of them had a  $BL \geq 10^{\text{th}}$  percentile according to INTERGROWTH-21<sup>st</sup> standards (630 children in the normal range on the CBCL were had a  $BL < 10^{\text{th}}$  percentile according to INTERGROWTH-21<sup>st</sup> standards). In ALSPAC stunting indices were better predictors of poor attention outcomes across all four measures than BW, wasting or asymmetry indices (Table 5.15). The strongest stunting index was  $BL < 10^{\text{th}}$  I-21<sup>st</sup>. A similar pattern was identified in INTERGROWTH-21<sup>st</sup>, in which stunting indices were identified as having the strongest predictive value. As with the other two cohorts,  $BL < 10^{\text{th}}$  I-21<sup>st</sup> was identified as the stunting index with the overall highest predictive values (Table 5.16). Comparatively across cohorts, birth anthropometric indices had the highest predictive value in Pelotas, followed by ALSPAC and then INTERGROWTH-21<sup>st</sup>.

**Table 5.14. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in Pelotas**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95%CI)       |
|------------------------------------------|-------------|-------------|-------|-------|-------------------|
| <b>BW indices</b>                        |             |             |       |       |                   |
| BW <2500g                                | 13.9%       | 91.3%       | 11.2% | 93.1% | 0.53 (0.49-0.56)  |
| SGA                                      | 23.2%       | 85.9%       | 11.4% | 93.5% | 0.54 (0.51-0.58)* |
| BW <10 <sup>th</sup> MGRS                | 25.6%       | 82.0%       | 10.1% | 93.4% | 0.54 (0.50-0.58)* |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 17.7%       | 91.0%       | 13.3% | 93.4% | 0.54 (0.51-0.58)* |
| <b>Stunting indices</b>                  |             |             |       |       |                   |
| BL <10 <sup>th</sup> MGRS                | 36.5%       | 72.3%       | 9.4%  | 93.6% | 0.54 (0.51-0.58)* |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 27.0%       | 81.9%       | 10.4% | 93.5% | 0.55 (0.51-0.58)* |
| HC <10 <sup>th</sup> MGRS                | 22.5%       | 84.3%       | 10.1% | 93.3% | 0.53 (0.50-0.57)  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 8.9%        | 92.7%       | 8.7%  | 92.9% | 0.51 (0.47-0.54)  |
| <b>Wasting indices</b>                   |             |             |       |       |                   |
| PI <10 <sup>th</sup> percentile          | 13.7%       | 90.3%       | 9.9%  | 93.0% | 0.52 (0.48-0.56)  |
| PI-for-age <10 <sup>th</sup> percentile  | 12.2%       | 90.5%       | 9.1%  | 93.0% | 0.51 (0.48-0.55)  |
| BMI <10 <sup>th</sup> percentile         | 14.8%       | 90.4%       | 10.8% | 93.1% | 0.53 (0.49-0.56)  |
| BMI-for-age <10 <sup>th</sup> percentile | 11.9%       | 90.4%       | 8.8%  | 92.9% | 0.51 (0.48-0.55)  |
| <b>Asymmetry indices</b>                 |             |             |       |       |                   |
| HC/BL >90 <sup>th</sup> percentile       | 13.3%       | 90.3%       | 9.7%  | 93.0% | 0.52 (0.48-0.56)  |
| HC/PI >90 <sup>th</sup> percentile       | 11.4%       | 90.1%       | 8.3%  | 92.9% | 0.51 (0.47-0.54)  |
| HC/BMI >90 <sup>th</sup> percentile      | 13.3%       | 90.3%       | 9.7%  | 93.0% | 0.52 (0.48-0.55)  |

\* = p&lt;.05; \*\* = p&lt;.001

**Table 5.15. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in ALSPAC**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>BW indices</b>                        |             |             |       |       |                  |
| BW <2500g                                | 5.0%        | 96.6%       | 15.1% | 89.2% | 0.51 (0.48-0.53) |
| SGA                                      | 10.6%       | 92.8%       | 15.3% | 89.4% | 0.52 (0.50-0.54) |
| BW <10 <sup>th</sup> MGRS                | 12.2%       | 92.1%       | 16.0% | 89.5% | 0.52 (0.50-0.55) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 7.2%        | 95.3%       | 15.8% | 89.3% | 0.51 (0.49-0.53) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL <10 <sup>th</sup> MGRS                | 9.2%        | 94.7%       | 17.4% | 89.5% | 0.52 (0.50-0.54) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 6.5%        | 96.6%       | 19.1% | 89.4% | 0.52 (0.49-0.54) |
| HC <10 <sup>th</sup> MGRS                | 14.2%       | 90.5%       | 15.5% | 90.5% | 0.51 (0.49-0.54) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 8.1%        | 95.4%       | 17.7% | 89.4% | 0.50 (0.48-0.52) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 11.4%       | 90.4%       | 12.6% | 89.3% | 0.51 (0.49-0.53) |
| PI-for-age <10 <sup>th</sup> percentile  | 9.9%        | 90.2%       | 11.1% | 89.2% | 0.50 (0.48-0.52) |
| BMI <10 <sup>th</sup> percentile         | 12.2%       | 90.8%       | 13.9% | 89.4% | 0.52 (0.49-0.54) |
| BMI-for-age <10 <sup>th</sup> percentile | 12.7%       | 90.1%       | 14.6% | 89.5% | 0.52 (0.50-0.54) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 10.8%       | 90.5%       | 12.2% | 89.2% | 0.51 (0.48-0.53) |
| HC/PI >90 <sup>th</sup> percentile       | 8.6%        | 89.8%       | 9.3%  | 89.0% | 0.49 (0.47-0.52) |
| HC/BMI >90 <sup>th</sup> percentile      | 11.6%       | 90.6%       | 13.0% | 98.4% | 0.51 (0.49-0.53) |

\* = p&lt;.05; \*\* = p&lt;.001



**Table 5.16. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in INTERGROWTH-21st**

| Variables                                | Sensitivity | Specificity | PPV  | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|------|-------|------------------|
| <b>BW indices</b>                        |             |             |      |       |                  |
| BW <2500g                                | 1.7%        | 93.5%       | 1.5% | 94.2% | 0.47 (0.40-0.54) |
| SGA                                      | 20.3%       | 78.5%       | 5.2% | 94.5% | 0.49 (0.42-0.57) |
| BW <10 <sup>th</sup> MGRS                | 21.7%       | 82.4%       | 6.8% | 94.7% | 0.52 (0.44-0.60) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 13.3%       | 88.1%       | 6.2% | 94.5% | 0.51 (0.43-0.59) |
| <b>Stunting indices</b>                  |             |             |      |       |                  |
| BL <10 <sup>th</sup> MGRS                | 15.0%       | 86.4%       | 6.1% | 94.5% | 0.50 (0.43-0.59) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 16.9%       | 90.5%       | 9.4% | 94.9% | 0.54 (0.46-0.62) |
| HC <10 <sup>th</sup> MGRS                | 15.0%       | 85.9%       | 6.0% | 94.5% | 0.50 (0.42-0.58) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 11.9%       | 93.1%       | 9.2% | 94.7% | 0.53 (0.45-0.60) |
| <b>Wasting indices</b>                   |             |             |      |       |                  |
| PI <10 <sup>th</sup> percentile          | 10.0%       | 89.9%       | 5.6% | 94.4% | 0.49 (0.42-0.57) |
| PI-for-age <10 <sup>th</sup> percentile  | 11.9%       | 90.3%       | 6.7% | 94.6% | 0.51 (0.43-0.59) |
| BMI <10 <sup>th</sup> percentile         | 6.7%        | 89.7%       | 3.7% | 94.2% | 0.48 (0.40-0.55) |
| BMI-for-age <10 <sup>th</sup> percentile | 10.2%       | 98.6%       | 5.4% | 94.5% | 0.50 (0.42-0.57) |
| <b>Asymmetry indices</b>                 |             |             |      |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 11.7%       | 90.5%       | 6.8% | 94.5% | 0.51 (0.43-0.59) |
| HC/PI >90 <sup>th</sup> percentile       | 11.7%       | 89.9%       | 6.4% | 94.5% | 0.51 (0.43-0.58) |
| HC/BMI >90 <sup>th</sup> percentile      | 10.0%       | 89.8%       | 5.5% | 94.4% | 0.50 (0.42-0.57) |

\* = p&lt;.05; \*\* = p&lt;.001

For cognitive outcomes, in Pelotas, stunting indices were better predictors all four measures (sensitivity, specificity, PPV and NPV) than BW, wasting or asymmetry indices. The stunting index with the strongest predictive value was HC <10<sup>th</sup> MGRS (Table 5.17). A similar pattern was identified in ALSPAC, with stunting indices being better predictors of poor cognitive outcomes all four measures than BW, wasting or asymmetry indices. The strongest stunting predictor was HC<10<sup>th</sup> I-21<sup>st</sup> (Table 5.18). A slightly different pattern was observed in INTERGROWTH-21<sup>st</sup>, which showed wasting to have better predictive value across all four measures than BW, stunting or asymmetry indices. The strongest wasting predictor was PI <10<sup>th</sup> percentile (Table 5.19). Across all three cohorts, birth anthropometric indices had the highest predictive value of attention and cognitive outcomes in Pelotas, followed by ALSPAC and then INTERGROWTH-21<sup>st</sup>.

**Table 5.17. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in Pelotas**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95%CI)        |
|------------------------------------------|-------------|-------------|-------|-------|--------------------|
| <b>BW indices</b>                        |             |             |       |       |                    |
| BW <2500g                                | 15.2%       | 92.4%       | 31.5% | 82.5% | 0.54 (0.51-0.57)*  |
| SGA                                      | 20.6%       | 86.6%       | 26.0% | 82.6% | 0.54 (0.51-0.56)*  |
| BW <10 <sup>th</sup> MGRS                | 27.8%       | 83.6%       | 28.1% | 83.4% | 0.56 (0.53-0.58)** |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 14.4%       | 91.5%       | 28.1% | 82.3% | 0.53 (0.50-0.55)*  |
| <b>Stunting indices</b>                  |             |             |       |       |                    |
| BL <10 <sup>th</sup> MGRS                | 38.0%       | 73.9%       | 25.1% | 83.9% | 0.56 (0.53-0.58)** |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 26.2%       | 82.9%       | 26.0% | 83.1% | 0.55 (0.52-0.57)** |
| HC <10 <sup>th</sup> MGRS                | 27.4%       | 86.3%       | 31.5% | 83.8% | 0.57 (0.54-0.60)** |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 13.1%       | 93.9%       | 33.0% | 82.5% | 0.53 (0.51-0.56)*  |
| <b>Wasting indices</b>                   |             |             |       |       |                    |
| PI <10 <sup>th</sup> percentile          | 13.5%       | 90.8%       | 25.1% | 82.1% | 0.52 (0.50-0.55)   |
| PI-for-age <10 <sup>th</sup> percentile  | 10.7%       | 90.5%       | 20.4% | 81.6% | 0.51 (0.48-0.53)   |
| BMI <10 <sup>th</sup> percentile         | 16.8%       | 91.6%       | 31.5% | 82.8% | 0.54 (0.52-0.57)*  |
| BMI-for-age <10 <sup>th</sup> percentile | 12.1%       | 90.8%       | 23.1% | 81.9% | 0.52 (0.49-0.54)   |
| <b>Asymmetry indices</b>                 |             |             |       |       |                    |
| HC/BL >90 <sup>th</sup> percentile       | 13.1%       | 90.8%       | 24.6% | 82.0% | 0.52 (0.50-0.54)   |
| HC/PI >90 <sup>th</sup> percentile       | 9.5%        | 89.9%       | 17.7% | 81.2% | 0.50 (0.47-0.52)   |
| HC/BMI >90 <sup>th</sup> percentile      | 14.5%       | 91.0%       | 27.1% | 82.3% | 0.53 (0.50-0.55)*  |

\* = p&lt;.05; \*\* = p&lt;.001

**Table 5.18. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in ALSPAC**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>BW indices</b>                        |             |             |       |       |                  |
| BW <2500g                                | 3.3%        | 97.0%       | 16.7% | 84.6% | 0.50 (0.45-0.55) |
| SGA                                      | 7.9%        | 93.4%       | 17.9% | 84.7% | 0.50 (0.45-0.55) |
| BW <10 <sup>th</sup> MGRS                | 7.2%        | 92.8%       | 15.5% | 84.6% | 0.50 (0.45-0.55) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 6.6%        | 95.8%       | 22.2% | 85.0% | 0.51 (0.46-0.56) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL <10 <sup>th</sup> MGRS                | 4.6%        | 95.2%       | 14.9% | 84.5% | 0.50 (0.45-0.55) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 4.0%        | 97.5%       | 22.2% | 84.7% | 0.51 (0.46-0.56) |
| HC <10 <sup>th</sup> MGRS                | 4.6%        | 96.0%       | 17.5% | 84.7% | 0.51 (0.46-0.56) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 4.0%        | 98.2%       | 28.6% | 84.9% | 0.51 (0.46-0.56) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 13.4%       | 88.6%       | 17.5% | 84.9% | 0.51 (0.46-0.56) |
| PI-for-age <10 <sup>th</sup> percentile  | 12.1%       | 88.7%       | 16.2% | 84.7% | 0.50 (0.45-0.55) |
| BMI <10 <sup>th</sup> percentile         | 10.1%       | 89.5%       | 14.9% | 84.6% | 0.50 (0.45-0.55) |
| BMI-for-age <10 <sup>th</sup> percentile | 12.1%       | 90.1%       | 18.2% | 85.0% | 0.51 (0.46-0.56) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 6.0%        | 93.6%       | 14.5% | 84.5% | 0.50 (0.45-0.55) |
| HC/PI >90 <sup>th</sup> percentile       | 10.7%       | 89.1%       | 15.1% | 84.6% | 0.50 (0.45-0.55) |
| HC/BMI >90 <sup>th</sup> percentile      | 11.4%       | 89.5%       | 16.5% | 84.8% | 0.51 (0.45-0.56) |

\* = p&lt;.05; \*\* = p&lt;.001

**Table 5.19. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in INTERGROWTH-21<sup>st</sup>.**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>BW indices</b>                        |             |             |       |       |                  |
| BW <2500g                                | 6.5%        | 93.5%       | 21.7% | 78.4% | 0.50 (0.46-0.54) |
| SGA                                      | 20.6%       | 79.0%       | 21.2% | 78.5% | 0.50 (0.46-0.54) |
| BW <10 <sup>th</sup> MGRS                | 19.1%       | 82.8%       | 23.4% | 78.8% | 0.51 (0.47-0.55) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 13.5%       | 88.4%       | 24.2% | 78.8% | 0.51 (0.47-0.52) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL <10 <sup>th</sup> MGRS                | 10.9%       | 85.0%       | 16.7% | 77.6% | 0.48 (0.44-0.52) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 8.8%        | 89.3%       | 18.3% | 78.1% | 0.49 (0.45-0.53) |
| HC <10 <sup>th</sup> MGRS                | 17.9%       | 86.9%       | 27.3% | 79.3% | 0.52 (0.48-0.57) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 8.4%        | 93.6%       | 26.4% | 78.9% | 0.51 (0.47-0.55) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 14.0%       | 91.8%       | 32.0% | 79.5% | 0.53 (0.48-0.57) |
| PI-for-age <10 <sup>th</sup> percentile  | 13.2%       | 90.6%       | 30.0% | 79.4% | 0.52 (0.48-0.57) |
| BMI <10 <sup>th</sup> percentile         | 14.0%       | 91.5%       | 31.1% | 79.4% | 0.52 (0.48-0.57) |
| BMI-for-age <10 <sup>th</sup> percentile | 12.3%       | 90.6%       | 26.4% | 79.1% | 0.52 (0.47-0.56) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 8.3%        | 89.0%       | 17.3% | 77.8% | 0.49 (0.45-0.53) |
| HC/PI >90 <sup>th</sup> percentile       | 13.1%       | 91.6%       | 30.0% | 79.2% | 0.52 (0.48-0.57) |
| HC/BMI >90 <sup>th</sup> percentile      | 12.7%       | 91.3%       | 28.7% | 79.1% | 0.52 (0.48-0.56) |

\* = p&lt;.05; \*\* = p&lt;.001

## 5.4 Summary of results

The aim of this chapter was to examine the association between indices of BW, stunting, wasting and asymmetry, and attention and cognitive development in childhood. For attention outcomes, there was consistency across cohorts, summarised below.

### 5.4.1 Summary of associations with attention

In the Pelotas and ALSPAC cohorts, BW (<10<sup>th</sup> percentile) and stunting (BL<10<sup>th</sup> percentile) had the strongest associations with poorer attention outcomes, which held after adjustment for multiple confounding variables. The ORs for BW<10<sup>th</sup> percentile ranged from 1.21 in Pelotas to 2.11 in ALSPAC. This means that the odds of children with a BW<10<sup>th</sup> percentile having a poorer attention score was 1.21-2.11 times that of children with normal BW. The ORs for BL<10<sup>th</sup> percentile ranged from 1.24 in Pelotas to 2.84 in ALSPAC. This means that the odds of children with a BL<10<sup>th</sup> percentile having a poorer attention score was 1.24-2.84 times that of children with normal BL. These were both small, but statistically significant effects. There were fewer associations in the INTERGROWTH-21<sup>st</sup> cohort, although stunting (BL) was consistently identified across all three cohorts as being a better predictor of poor attention outcomes, compared to BW, wasting or asymmetry indices.

### 5.4.2 Summary of associations with cognition

There was less consistency in the cognitive outcomes. In Pelotas, indices of BW, stunting, wasting and asymmetry were all associated with poor cognitive outcomes after adjustment for multiple confounders. For the stunting indices, HC was more strongly associated with poorer cognitive outcome than BL. The asymmetry index identified as significantly associated with poorer cognitive outcomes was HC/BMI >90<sup>th</sup> percentile (evidence of fetal circulatory redistribution; FCR). There were fewer associations identified in ALSPAC, with poorer cognitive outcomes associated with BW only. There were no associations in the INTERGROWTH-21<sup>st</sup> cohort. The sensitivity and specificity analyses showed that stunting (HC) was the strongest

predictor of poor cognitive outcomes in both the Pelotas and ALSPAC cohorts; however in INTERGROWTH-21<sup>st</sup> the strongest predictor of poor cognitive outcome was PI, an index of wasting.

### **5.4.3 Consistencies across cohorts**

Across both the attention and cognitive analyses, a consistent pattern was identified whereby the strongest effects were shown in Pelotas, followed by ALSPAC and then INTERGROWTH-21<sup>st</sup>. There was some agreement between the Pelotas and ALSPAC cohorts, with INTERGROWTH-21<sup>st</sup> showing fewer effects. Although OLR analysis with full adjustment is highly conservative, few effects were also identified in unadjusted analyses in INTERGROWTH-21<sup>st</sup>. One reason for this may be that there is some heterogeneity between the associations across the different INTERGROWTH-21<sup>st</sup> sites (UK, Italy, Brazil, India, and Kenya), and including all sites in one analysis thus obscures differential effects across sites. Such differences could arise from variation in confounding structures, for example, the social patterning of caesarean sections. An alternative explanation may be that as the INTERGROWTH-21<sup>st</sup> cohort was selected as a low-risk cohort, within these healthy mothers there are few associations between small size at birth and attention and cognitive development. This could be due to the fact that as the identification of impaired fetal growth is statistical (based on the 10<sup>th</sup> percentile cut-off) these low-risk neonates are actually normally grown, but constitutionally small. To determine which explanation may be correct, potential differences across the INTERGROWTH-21<sup>st</sup> sites and differences between descriptive (no selection criteria) and low-risk cohorts will be explored in Studies I and II respectively, of Chapter 6.

Another pattern identified across cohorts was that there appeared to be stronger associations for birth indices using MGRS standards (OLR analyses), but stronger predictive value for those using INTERGROWTH-21<sup>st</sup> standards (sensitivity and specificity analyses). This was particularly true of attention outcomes. One reason for this may be that MGRS indices have

more power, due to a higher prevalence of children being classified as 'small' by these references, compared to INTERGROWTH-21<sup>st</sup>. An alternative explanation may be that whilst INTERGROWTH-21<sup>st</sup> indices have the better predictive value for impaired outcomes, associations are identified as stronger for MGRS indices, due to the fact that the MGRS indices do not account for GA at birth, and thus include a larger proportion a preterm neonates than INTERGROWTH-21<sup>st</sup> indices. Although GA at birth was statistically adjusted for in OLR, there may be some residual effects. For example, as preterm delivery has been associated with attention and cognitive impairment in childhood<sup>14</sup>, a higher proportion of preterm deliveries may enhance the associations.

## **5.5 Conclusions**

Of all the birth indices examined, stunting (specifically BL) was most strongly associated with poorer attention outcomes (albeit not statistically significant in INTERGROWTH-21<sup>st</sup>), and had stronger predictive value for poor attention outcomes across all three cohorts, than indices of BW, wasting or asymmetry. These were small, but statistically significant effects. The findings were less consistent across cohorts for poor cognitive outcomes; however stunting (specifically HC) in Pelotas and ALSPAC, and wasting (PI) in INTERGROWTH-21<sup>st</sup>, had the strongest predictive value for poor cognitive outcomes. Further examination of potential differences in the INTERGROWTH-21<sup>st</sup> cohort is required to 1) clarify any differences across sites and 2) examine potential differences between descriptive (no selection criteria) and low-risk cohorts. These points will be examined in turn, in Chapter 6, in two studies, Study I and Study 2.



## 5.6 References

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## **6 Cross-site and cross-cohort comparisons of the associations between birth anthropometric indices and attention and cognitive development**

### **Chapter outline**

#### **6.1 Introduction**

##### 6.1.1 Hypotheses

#### **6.2 Methods**

##### 6.2.1 Sample characteristics

##### 6.2.2 Primary measures

##### 6.2.3 Confounding variables

##### 6.2.4 Statistical analysis

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#### **6.3 Results**

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##### 6.3.2 Study II: Comparison between descriptive and low-risk cohorts from the same location

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##### 6.4.2 Summary of Study II

##### 6.4.3 How this chapter builds on previous chapters

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#### **6.6 References**

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## 6.1 Introduction

Chapter 5 showed associations between indices of impaired fetal growth and attention and cognitive outcomes in the Pelotas and ALSPAC cohorts, but not in the INTERGROWTH-21<sup>st</sup> cohort. There are two possible reasons suggested for this. Firstly, it is possible that there are differences in the strength and/or direction of associations across INTERGROWTH-21<sup>st</sup> sites. This may be due to underlying differences in confounding structures between sites. An alternative explanation may be that as the mothers in the INTERGROWTH-21<sup>st</sup> sample were specifically selected as being low-risk, their infants, even those that fall below the statistical level of growth impairment, go on to develop normally.

This chapter therefore explores the INTERGROWTH-21<sup>st</sup> cohort further in two studies (Study I and Study II), examining both alternative explanations above, respectively. Study I aims to examine the variability between INTERGROWTH-21<sup>st</sup> study sites, by examining cross-site differences in the associations between fetal growth impairment and attention and cognitive development. Study II aims to explore the variability between descriptive (no selection criteria) and low-risk cohorts within sites, comparing cohorts within the same geographical location. Specifically, comparisons in this sub-study will be made between associations in the 2004 Pelotas Birth Cohort and the Pelotas subsample of the INTERGROWTH-21<sup>st</sup> cohort (both in Brazil) and the ALSPAC cohort and the UK subsample of the INTERGROWTH-21<sup>st</sup> cohort (both in the UK).

### 6.1.1 Hypotheses

Based on previous research, it is hypothesised that:

- 1) Associations in LMICs will be stronger than in HICs
- 2) There will be more associations in descriptive compared to low-risk samples

## 6.2 Methods

### 6.2.1 Sample characteristics

Three cohorts were included in the analysis, the Pelotas 2004 Birth Cohort, the ALSPAC birth cohort, and the INTERGROWTH-21<sup>st</sup> cohort. The INTERGROWTH-21<sup>st</sup> sites are shown in Figure 6.1, with comparative information from the collection sites presented in Table 6.1. All children for whom at least one birth anthropometric index and attention or cognitive outcomes were available were included in the analysis (88.6% of the initial Pelotas 2004 cohort, 55.6% of the initial ALSPAC cohort, and 65.3% of the eligible INTERGROWTH-21<sup>st</sup> cohort). Information is presented on each of the cohorts in Chapter 3 (sections 3.1-3.3).



**Figure 6.1.** The sites of the INTERGROWTH-21<sup>st</sup> Project neurodevelopmental assessments. High-income country = red dot; middle-income country = yellow dot; low-income country = blue dot.

**Table 6.1. Comparative population information from INTERGROWTH-21st neurodevelopmental assessment sites**

| Site          | World Bank Classification | City                      | Region/State      | City population                    | City GDP <sup>i</sup>        | Hospitals                                                                                                                                                                                                            | Additional information                                                                                                                                                                                        |
|---------------|---------------------------|---------------------------|-------------------|------------------------------------|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>UK</b>     | High-income               | Oxford                    | Oxfordshire       | 150,000                            | US\$53 billion               | John Radcliffe Hospital                                                                                                                                                                                              | Oxford has a large proportion of young, middle-class, well-educated, professional families. The main economic activities are services (including tourism, retail and two universities) and car manufacturing. |
| <b>Italy</b>  | High-income               | Turin                     | Piemonte          | 910,500                            | US\$58 billion               | Azienda Ospedaliera OIRM—S. Anna                                                                                                                                                                                     | Turin is a major industrial centre, known primarily for the aerospace and car manufacturing industries.                                                                                                       |
| <b>Brazil</b> | Upper-middle income       | Pelotas                   | Rio Grande do Sul | 340,000                            | US\$23 billion               | Hospital Miguel Piltcher; Hospital São Francisco de Paula; Hospital Escola UFPEL; Santa Casa do Misericórdia                                                                                                         | Pelotas is a relatively wealthy Southern Brazilian city. The main economic activities in Pelotas are agriculture (predominantly rice and cattle) and services (including two Universities).                   |
| <b>India</b>  | Lower-middle income       | Nagpur                    | Maharashtra       | 2.2 million                        | US\$15 billion               | Ketkar Hospital; Avanti Hospital; Mulik Hospital & Research Center; Renuka Nursing Home; Om Women's Hospital; Somani Nursing Home; Saboo Nursing Home; Avantika Hospital; Nandlok Hospital; Gurukrupa Maternity Home | Nagpur is an important trading location in the Vidarbha region. It is a main centre of education and politics, and has good health care services.                                                             |
| <b>Kenya</b>  | Low-income                | Parklands suburb, Nairobi | Nairobi           | 40,000 (3.5million <sup>ii</sup> ) | US\$12 billion <sup>ii</sup> | Aga Khan University Hospital<br>Avenue Hospital<br>M.P. Shah Hospital                                                                                                                                                | Parklands is a wealthy suburb in the city of Nairobi. It is a non-malaria endemic area, mostly home to affluent Kenyan families.                                                                              |

<sup>i</sup> approximate value; <sup>ii</sup> total Nairobi

### **6.2.2 Primary measures**

This analysis uses primary birth anthropometric indices for which data was available in each of the cohorts, including birth weight (BW), stunting, wasting and asymmetry indices (see Chapter 5). Information on birth anthropometric measurement methods and how these indices were derived is presented in Chapter 3 (sections 3.1.2, 3.2.2, 3.3.2 and 3.4).

Follow-up assessments of attention include the CBCL in the INTERGROWTH-21<sup>st</sup> cohort (at 2 years), the CBCL in the Pelotas 2004 birth cohort (at 4 years), and the SDQ in the ALSPAC cohort (at 6 years). Follow-up assessments of cognition include the INTER-NDA in the INTERGROWTH-21<sup>st</sup> cohort (at 2 years), and the WPPSI-R in the Pelotas 2004 and the ALSPAC cohorts (at 4 years). More information on the attention and cognitive assessment procedures are presented in Chapter 3 (sections 3.1.2, 3.2.2, and 3.3.2).

### **6.2.3 Confounding variables**

Data were collected on a range of demographic, maternal, gestational, perinatal, and childhood variables. More information on the collection and classification of confounding variables is presented in Chapter 3 (Sections 3.2.1, 3.2.3 and 3.3.3).

### **6.2.4 Statistical analysis**

#### **6.2.4.1 Study I**

First, birth anthropometric index\*site interactions were assessed using ordinal logistic regressions (OLRs) to: 1) examine whether associations between indices of impaired fetal growth and attention and cognitive outcomes differed by INTERGROWTH-21<sup>st</sup> site; and 2) justify further examination of differences between sites. The prevalence and descriptive statistics of maternal and child characteristics were calculated for each site, and between-site differences examined using univariate ANOVAs and Pearson  $\chi^2$  tests. Ryan-Einot-Gabriel-Welsch Range (REGWQ) post-hoc analyses of homogenous subsets were used to determine which sites differed significantly from others. The prevalences of birth anthropometric indices and poor

attention and cognitive outcomes were calculated for each site, with chi-squared analyses used to identify differences across site. As in Chapter 5, the primary analysis to examine the associations between birth anthropometric indices and attention and cognitive outcomes consisted of hierarchical modelling using OLR, separately for each site. Due to the loss of power associated with dividing the full cohort by site (UK:  $N=168$ ; Italy:  $N=206$ ; Brazil:  $N=108$ ; Kenya:  $N=319$ ; India:  $N=252$ ; Figure 6.1), modelling was adjusted only for age-at-follow up.

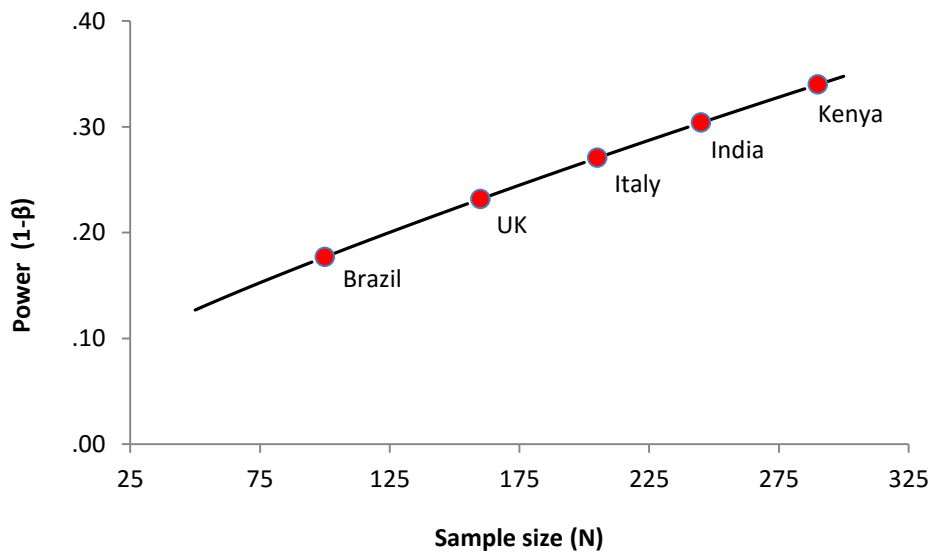


**Figure 6.2. Power analysis (1-β) of INTERGROWTH-21<sup>st</sup> sites. Estimates based on OR=1.2.**

Finally, to compare the ability of birth anthropometric indices to predict poor attention or cognitive outcomes in childhood across the different sites, sensitivity, specificity and receiver-operating characteristic (ROC) analyses were conducted.

#### 6.2.4.2 Study II

Differences in maternal and child characteristics between the INTERGROWTH-21<sup>st</sup> UK site and the ALSPAC cohort, and between the INTERGROWTH-21<sup>st</sup> Brazil site and the Pelotas 2004 birth cohort were assessed using univariate ANOVAs and Pearson  $\chi^2$  tests. Differences in the prevalence of birth anthropometric indices and poor attention and cognitive outcomes were analysed using chi-squared analyses. The pattern of the associations between birth anthropometric indices and attention and cognitive outcomes were compared between a) the INTERGROWTH-21<sup>st</sup> UK site and the ALSPAC cohort, and b) the INTERGROWTH-21<sup>st</sup> Brazil site and the Pelotas 2004 birth cohort.

All analyses were performed using IBM SPSS Statistics for Windows 21.0<sup>1</sup>. Further statistical considerations for statistical analyses are presented in Chapter 3 (section 3.6).

### 6.3 Results

#### 6.3.1 Study I: Comparison between INTERGROWTH-21<sup>st</sup> sites

The total INTERGROWTH-21<sup>st</sup> sample across the UK, Italy, Brazil, India and Kenya sites consisted of 2803 neonates. Of these, 1649 infants were eligible for the INTER-NDA at the time of data freezing. The INTER-NDA and CBCL were conducted at the 24 month follow-up ( $M=24.85$ ,  $SD=2.02$  months), with valid data CBCL (attention) data on 1076 children (65.3% of the eligible sample) and INTER-NDA (cognitive) data on 1066 children (64.6% of eligible sample). Sample sizes differed across site from 108 to 319 (UK:  $N=168$ ; Italy:  $N=206$ ; Brazil:  $N=108$ ; Kenya:  $N=319$ ; India:  $N=252$ )<sup>i</sup>. OLR analyses including birth anthropometric indices\*site as an interaction term, showed that site modified the association between all birth anthropometric indices and attention outcomes (with the exception of BMI<10<sup>th</sup> percentile) and one birth anthropometric index and cognitive outcome (BL<10<sup>th</sup> percentile using MGRS standards; Table S6.1). This

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<sup>i</sup> Due to cut-off date for data analysis the Italy and Brazil sites had yet to complete data collection. These samples are thus a subset of what will be the full final sample.



justified separation of further analyses by site for the attention outcome (however cognitive outcome was also included for consistency).

Cross-site comparison of maternal and child characteristics showed that the INTERGROWTH-21<sup>st</sup> sites differed on all maternal and child characteristics (with the exception of the prevalence of preterm delivery (<37 weeks), APGAR score <7 and child sex; Table S6.2). Post-hoc analyses showed mothers had significantly more years of education in UK and India (16.26 and 16.14 years, respectively), and less in Italy and Brazil (13.79 and 13.86 years, respectively), compared to other sites. Maternal age at delivery was significantly higher in the UK (30.58 years) and lower in India (27.15 years) than the rest of the sites, and maternal BMI at enrolment was lower in the UK, Brazil and India (22.46-23.41 kg/m<sup>2</sup>) than it was in Kenya and Italy (24.03 kg/m<sup>2</sup>). Rates of caesarean section differed markedly between sites, ranging from 16.1% in the UK to 85.8% in Brazil. The prevalence of breastfeeding duration less than 6 months also differed significantly, from 2.1% and 6.4% in India and Kenya, respectively, to 24.8%-32.1% in the other sites. Figure 6.3 shows the prevalence (%) of maternal and child characteristics across the INTERGROWTH-21<sup>st</sup> sites.

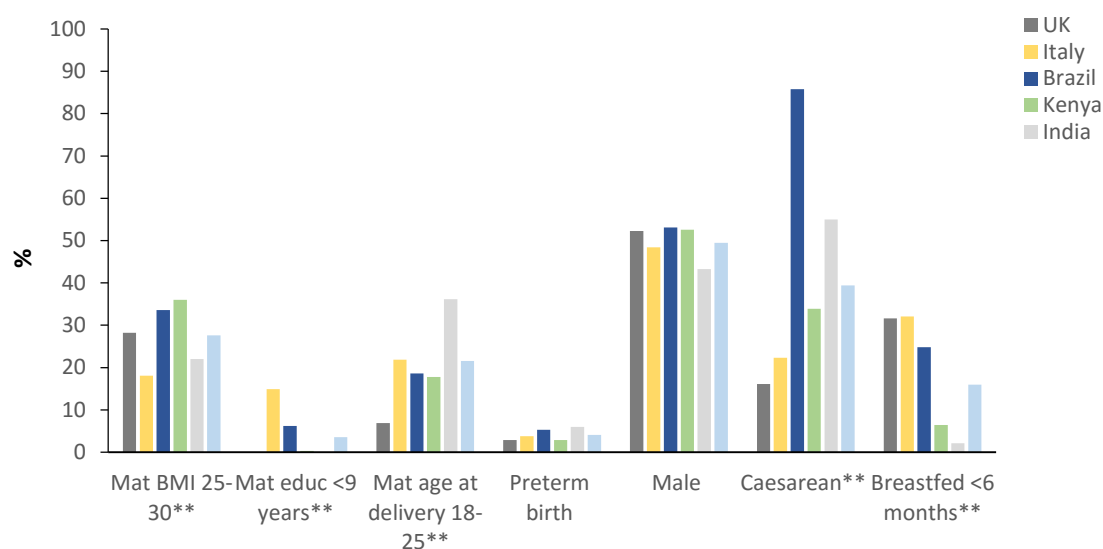


**Figure 6.3. Prevalence (%) of maternal and child characteristics across INTERGROWTH-21st sites and total. \*= $p < .05$ ; \*\*= $p < .001$  difference between groups (chi-square analysis)**

The prevalence of birth anthropometric indices below cut-off points for all of the birth indices (BW, stunting, wasting and asymmetry) also differed between INTERGROWTH-21<sup>st</sup> sites (Table 6.2; Figure 6.4). The UK generally had larger neonates and India had smaller neonates than the other sites. By birth indices, the UK had the lowest prevalence of LBW indices (3.4-8.0%), and India had the highest prevalence of LBW indices (10.9%-39.4%). The UK also had a generally lower rate of stunting as measured by BL (5.3%) than all other sites (7.5-20.4%), and India had a higher rate of stunting as measured by HC (15.2-30.9%) compared to all other sites (2.7-5.8%). There was also a higher prevalence of wasting in India (20.2-22.7%) than in other sites (0.9-10.1%).

The rates of asymmetry also differed between sites. India had the highest rate of both high HC/PI and HC/BMI ratios (19.5-19.9%), compared to other sites (1.8-10.0%). Brazil had the highest rate of high HC/BL ratio (18.6%), compared to other sites (2.8%-13.9%), reflecting the significantly lower BL, but normal HC in Brazil (see Table S6.2).

**Table 6.2. Frequency n(%) and chi-squared analyses of birth indices by site**

| Variable                                 | UK (N=168) | Italy (N=206) | Brazil (N=108) | Kenya (N=319) | India (N=252) | Total (N=1053) | $\chi^2$ | <i>p</i> |
|------------------------------------------|------------|---------------|----------------|---------------|---------------|----------------|----------|----------|
| <b>Birth weight indices</b>              |            |               |                |               |               |                |          |          |
| BW <2500g                                | 6 (3.4)    | 9 (4.2)       | 5 (4.4)        | 23 (6.7)      | 30 (10.6)     | 73 (6.5)       | 13.37    | .010*    |
| SGA                                      | 13 (7.5)   | 40 (18.8)     | 15 (13.3)      | 60 (17.7)     | 111 (39.4)    | 239 (21.3)     | 82.44    | <.001**  |
| BW <10 <sup>th</sup> MGRS                | 14 (8.0)   | 27 (12.6)     | 13 (11.5)      | 42 (12.3)     | 106 (37.6)    | 202 (17.9)     | 100.38   | <.001**  |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 7 (4.0)    | 25 (11.6)     | 8 (7.1)        | 34 (9.9)      | 61 (21.6)     | 135 (12.0)     | 39.28    | <.001**  |
| <b>Stunting indices</b>                  |            |               |                |               |               |                |          |          |
| BL < 10 <sup>th</sup> MGRS               | 9 (5.3)    | 23 (10.7)     | 23 (20.4)      | 47 (13.9)     | 54 (19.1)     | 156 (13.9)     | 22.89    | <.001**  |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 9 (5.3)    | 16 (7.5)      | 12 (10.6)      | 45 (13.4)     | 31 (11.0)     | 113 (10.1)     | 10.24    | .037*    |
| HC <10 <sup>th</sup> MGRS                | 14 (8.1)   | 19 (8.9)      | 10 (8.8)       | 31 (9.1)      | 87 (30.9)     | 161 (14.4)     | 83.23    | <.001**  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 10 (5.8)   | 6 (2.8)       | 3 (2.7)        | 18 (5.4)      | 43 (15.2)     | 80 (7.2)       | 39.18    | <.001**  |
| <b>Wasting indices</b>                   |            |               |                |               |               |                |          |          |
| PI <10 <sup>th</sup> percentile          | 5 (2.9)    | 14 (6.5)      | 1 (0.9)        | 27 (8.0)      | 64 (22.7)     | 111 (9.9)      | 75.50    | <.001**  |
| PI-for-age <10 <sup>th</sup> percentile  | 8 (4.7)    | 16 (7.5)      | 2 (1.8)        | 23 (6.8)      | 60 (21.3)     | 109 (9.8)      | 60.05    | <.001**  |
| BMI <10 <sup>th</sup> percentile         | 3 (1.8)    | 13 (6.0)      | 4 (3.5)        | 29 (8.6)      | 62 (22.0)     | 111 (9.9)      | 68.22    | <.001**  |
| BMI-for-age <10 <sup>th</sup> percentile | 6 (3.5)    | 17 (8.0)      | 3 (2.7)        | 30 (8.9)      | 57 (20.2)     | 113 (10.1)     | 48.26    | <.001**  |
| <b>Asymmetry indices</b>                 |            |               |                |               |               |                |          |          |
| HC/BL >90 <sup>th</sup> percentile       | 12 (7.0)   | 23 (10.8)     | 21 (18.6)      | 47 (13.9)     | 8 (2.8)       | 111 (9.9)      | 33.00    | <.001**  |
| HC/PI >90 <sup>th</sup> percentile       | 7 (4.1)    | 15 (7.0)      | 2 (1.8)        | 32 (9.4)      | 55 (19.5)     | 111 (9.9)      | 45.91    | <.001**  |
| HC/BMI >90 <sup>th</sup> percentile      | 4 (2.3)    | 14 (6.6)      | 3 (2.7)        | 34 (10.0)     | 56 (19.9)     | 111 (9.9)      | 51.48    | <.001**  |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21st = INTERGROWTH-21st growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

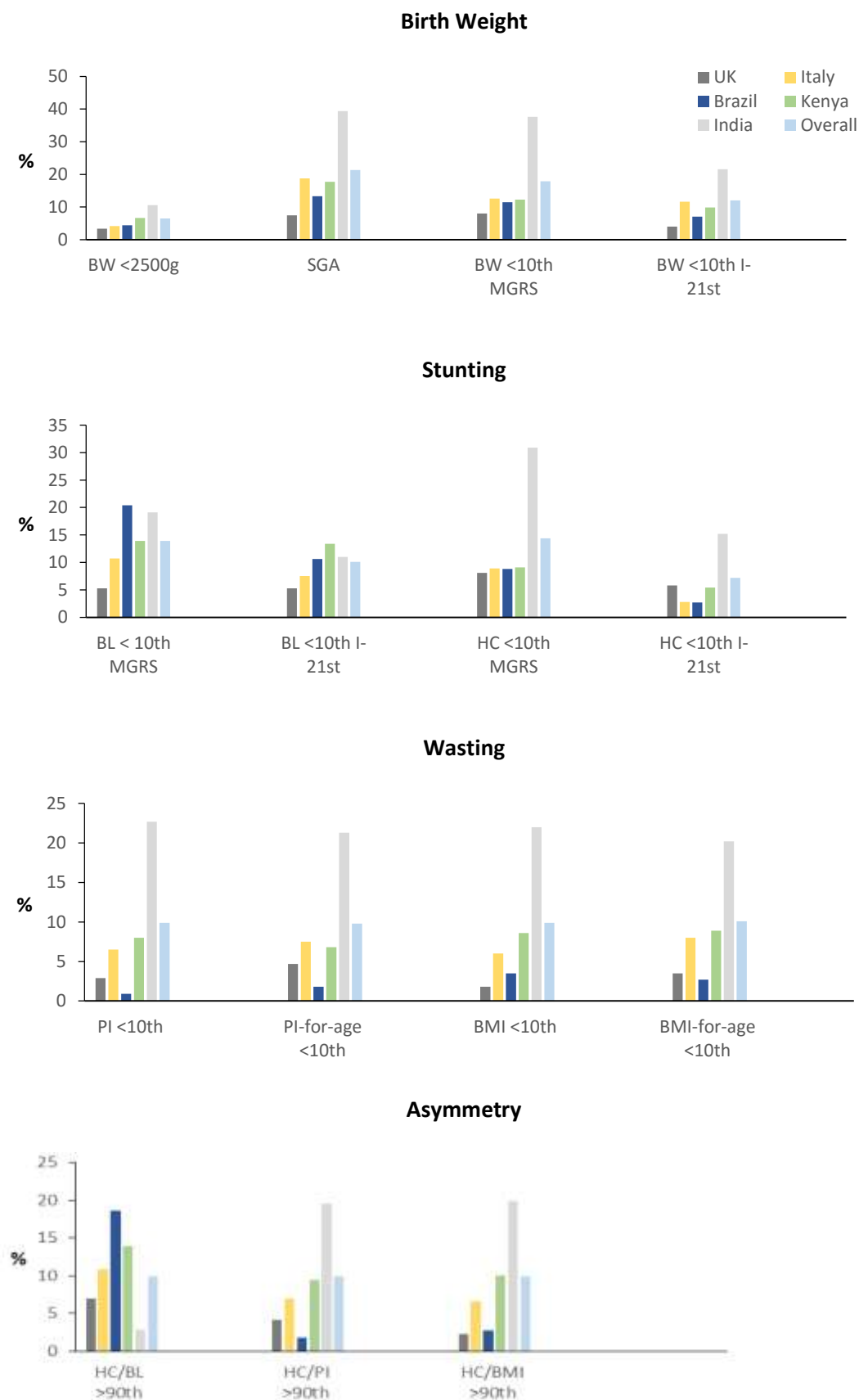


Figure 6.4. Prevalence (%) of birth anthropometric indices by site

The age at follow-up differed between the sites (Table 6.3). Brazilian children were on average 5 months older at completion (29.7 months) compared to the other sites (24.05-24.6 months; Table 6.3). The median attention scores also differed between sites ( $\chi^2 = 79.81, p < .001$ ). India had a significantly higher attention score (indicating poorer attention) compared to the other sites, and a higher prevalence of attention impairment by dichotomous outcome (11.1%). The lowest prevalence of attention impairment was identified in Italy (0.5%). A significantly higher mean cognitive Z-score was identified in Brazilian children ( $Z = 0.63$ ), indicating better cognitive outcomes, compared to all other sites ( $Z = -0.15$ - $0.01$ ). After adjustment for sample variation in age at assessment (by calculating Z-scores within-site), India had the highest rate of cognitive impairment (28.0%). The lowest rate of cognitive impairment was identified in Brazil (14.2%). These baseline differences must be considered when examining differences in associations between sites.

**Table 6.3. Mean score, between-subjects tests, frequency n(%) and chi-squared analyses of attention and cognitive impairment by site**

| Variable                         | UK                        | Italy                     | Brazil                    | Kenya                     | India                     | Total        | $F/\chi^2$         | $p$     |
|----------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|--------------|--------------------|---------|
| <b>Age at follow-up (months)</b> | 24.38 (1.18) <sup>1</sup> | 24.57 (0.74) <sup>1</sup> | 29.67 (2.47) <sup>2</sup> | 24.42 (1.05) <sup>1</sup> | 24.05 (0.94) <sup>3</sup> | 24.87 (2.02) | 491.67             | <.001** |
| <b>Attention</b>                 |                           |                           |                           |                           |                           |              |                    |         |
| Mean score                       | 2.91 (1.72) <sup>1</sup>  | 2.58 (1.50) <sup>1</sup>  | 2.93 (1.78) <sup>1</sup>  | 2.53 (2.16) <sup>1</sup>  | 3.89 (2.20) <sup>2</sup>  | 2.97 (2.04)  | 79.81 <sup>a</sup> | <.001** |
| Impairment prevalence            | 6 (4.1%)                  | 2 (0.5%)                  | 4 (3.5%)                  | 19 (5.6%)                 | 30 (11.1%)                | 60 (5.6%)    | 27.04              | <.001** |
| <b>Cognition<sup>b</sup></b>     |                           |                           |                           |                           |                           |              |                    |         |
| Mean score                       | -0.03 (0.88) <sup>1</sup> | -0.10 (1.01) <sup>1</sup> | 0.63 (0.44) <sup>2</sup>  | -0.15 (1.05) <sup>1</sup> | 0.01 (1.07) <sup>1</sup>  | 0.00 (1.00)  | 14.22 <sup>b</sup> | <.001** |
| Impairment prevalence            | 34 (20.1%)                | 36 (19.5%)                | 16 (14.2%)                | 71 (20.0%)                | 73 (28.0%)                | 230 (21.6%)  | 10.75              | .030*   |

<sup>a</sup> for non-normally distributed outcome, between-subjects test was Kruskal-Wallis H, followed by post-hoc Mann-Whitney U tests (adjustment of familywise error rate using Bonferroni adjustment); <sup>b</sup> for normally distributed outcome, between subject test was ANOVA, followed Ryan-Einot-Gabriel-Welsch Range (REGWQ) post-hoc analyses homogeneous subsets; <sup>1,2,3</sup> = homogenous subsets; Impairments = CBCL  $t$  score  $\geq 67$ ; INTER-NDA score  $>1SD$  below mean \* =  $p < .05$ ; \*\*= $p < .001$

**6.3.1.1 Association between birth anthropometric indices and attention outcomes**

To assess the unadjusted associations between birth anthropometric indices and attention outcomes, OLR analyses were conducted separately for the INTERGROWTH-21<sup>st</sup> sites. There were some differences identified in associations between sites (Table 6.4; Table 6.5). Significant associations were identified between attention outcomes and the following indices: BL<10<sup>th</sup> percentile MGRS in UK, BL<10<sup>th</sup> percentile I-21<sup>st</sup> in Brazil, HC<10<sup>th</sup> percentile MGRS in India, and HC/BL >90<sup>th</sup> percentile in Kenya.

**Table 6.4. Unadjusted associations between birth growth indices and higher attention score in childhood in UK, Italy and Brazil**

| Variables                                | UK                       |              | Italy             |          | Brazil                     |              |
|------------------------------------------|--------------------------|--------------|-------------------|----------|----------------------------|--------------|
|                                          | OR (95%CI)               | <i>p</i>     | OR (95%CI)        | <i>p</i> | OR (95%CI)                 | <i>p</i>     |
| <b>Birth weight indices</b>              |                          |              |                   |          |                            |              |
| BW <2500g                                | 4.26 (0.69-26.32)        | .119         | 3.70 (0.97-14.17) | .056     | 0.86 (0.15-5.15)           | .872         |
| SGA                                      | 2.04 (0.64-6.52)         | .231         | 0.97 (0.50-1.86)  | .919     | 0.47 (0.19-1.15)           | .097         |
| BW <10 <sup>th</sup> MGRS                | 2.05 (0.64-6.54)         | .225         | 0.96 (0.45-2.05)  | .911     | 0.80 (0.29-2.16)           | .656         |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.49 (0.34-6.53)         | .599         | 0.90 (0.38-2.14)  | .818     | 0.42 (0.13-1.38)           | .154         |
| <b>Stunting indices</b>                  |                          |              |                   |          |                            |              |
| BL < 10 <sup>th</sup> MGRS               | <b>6.78 (1.50-30.59)</b> | <b>.013*</b> | 1.34 (0.62-2.92)  | .454     | 1.28 (0.56-2.91)           | .553         |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.91 (0.45-8.15)         | .384         | 1.10 (0.41-2.97)  | .850     | <b>3.09 (1.03-9.26)</b>    | <b>.044*</b> |
| HC <10 <sup>th</sup> MGRS                | 2.17 (0.63-7.47)         | .218         | 2.01 (0.82-4.89)  | .126     | 2.86 (0.86-9.55)           | .086         |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.10 (0.28-4.39)         | .891         | 3.11 (0.61-15.89) | .174     | 4.50 (0.57-35.42)          | .153         |
| <b>Wasting indices</b>                   |                          |              |                   |          |                            |              |
| PI <10 <sup>th</sup> percentile          | 1.83 (0.28-12.02)        | .531         | 0.95 (0.35-2.57)  | .915     | 6.84 (0.38-124.36)         | .194         |
| PI-for-age <10 <sup>th</sup> percentile  | 1.72 (0.47-6.30)         | .411         | 0.68 (0.25-1.83)  | .448     | <b>12.14 (1.38-106.43)</b> | <b>.024*</b> |
| BMI <10 <sup>th</sup> percentile         | 2.86 (0.31-26.50)        | .355         | 1.87 (0.66-5.29)  | .236     | 1.74 (0.24-12.83)          | .588         |
| BMI-for-age <10 <sup>th</sup> percentile | 1.29 (0.27-6.08)         | .750         | 0.74 (0.29-1.90)  | .536     | 4.49 (0.57-35.37)          | .154         |
| <b>Asymmetry indices</b>                 |                          |              |                   |          |                            |              |
| HC/BL >90 <sup>th</sup> percentile       | 0.52 (0.15-1.75)         | .289         | 0.75 (0.34-1.65)  | .475     | 0.61 (0.26-1.46)           | .268         |
| HC/PI >90 <sup>th</sup> percentile       | 1.61 (0.40-6.45)         | .505         | 0.91 (0.31-2.66)  | .862     | 0.43 (0.04-3.43)           | .475         |
| HC/BMI >90 <sup>th</sup> percentile      | 2.03 (0.34-12.33)        | .440         | 0.58 (0.20-1.66)  | .309     | 0.29 (0.05-1.75)           | .178         |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21st = INTERGROWTH-21st growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = *p*<.05; \*\*=*p*<.001 (significant associations in bold)



**Table 6.5. Unadjusted associations between birth growth indices and higher attention score in childhood in India and Kenya**

| Variables                                | India                   |              | Kenya                   |              |
|------------------------------------------|-------------------------|--------------|-------------------------|--------------|
|                                          | OR (95%CI)              | <i>p</i>     | OR (95%CI)              | <i>p</i>     |
| <b>Birth weight indices</b>              |                         |              |                         |              |
| BW <2500g                                | 0.54 (0.27-1.06)        | .073         | 0.64 (0.31-1.33)        | .235         |
| SGA                                      | 0.66 (0.43-1.01)        | .057         | 0.82 (0.50-1.34)        | .425         |
| BW <10 <sup>th</sup> MGRS                | 0.85 (0.55-1.31)        | .091         | 0.66 (0.37-1.17)        | .153         |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.91 (0.55-1.52)        | .726         | 0.59 (0.32-1.09)        | .091         |
| <b>Stunting indices</b>                  |                         |              |                         |              |
| BL < 10 <sup>th</sup> MGRS               | 0.69 (0.41-1.18)        | .175         | 0.86 (0.49-1.52)        | .602         |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.01 (0.51-2.03)        | .972         | 1.18 (0.66-2.11)        | .582         |
| HC <10 <sup>th</sup> MGRS                | <b>0.59 (0.38-0.94)</b> | <b>.027*</b> | 0.78 (0.41-1.47)        | .440         |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.73 (0.40-1.33)        | .299         | 0.66 (0.30-1.48)        | .314         |
| <b>Wasting indices</b>                   |                         |              |                         |              |
| PI <10 <sup>th</sup> percentile          | 0.85 (0.52-1.38)        | .503         | 0.73 (0.37-1.43)        | .359         |
| PI-for-age <10 <sup>th</sup> percentile  | 1.19 (0.72-1.97)        | .501         | 0.50 (0.24-1.03)        | .060         |
| BMI <10 <sup>th</sup> percentile         | 0.82 (0.50-1.33)        | .412         | 0.81 (0.42-1.56)        | .535         |
| BMI-for-age <10 <sup>th</sup> percentile | 1.21 (0.73-2.01)        | .453         | 0.58 (0.31-1.08)        | .087         |
| <b>Asymmetry indices</b>                 |                         |              |                         |              |
| HC/BL >90 <sup>th</sup> percentile       | 0.76 (0.24-2.44)        | .642         | <b>1.76 (1.01-3.08)</b> | <b>.048*</b> |
| HC/PI >90 <sup>th</sup> percentile       | 0.88 (0.52-1.46)        | .612         | 0.56 (0.30-1.04)        | .065         |
| HC/BMI >90 <sup>th</sup> percentile      | 0.83 (0.50-1.39)        | .488         | 0.69 (0.37-1.29)        | .242         |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21st = INTERGROWTH-21st growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* =  $p < .05$ ; \*\*= $p < .001$  (significant associations in bold)

Due to limited power to detect statistically significant associations, the pattern of ORs was examined across sites to identify possible variation (Figure 6.5). Some variation was identified across sites, particularly for stunting indices. Stunting was shown to be positively associated with poor attention outcomes in the UK, Italy and Brazil, but not in India and Kenya.

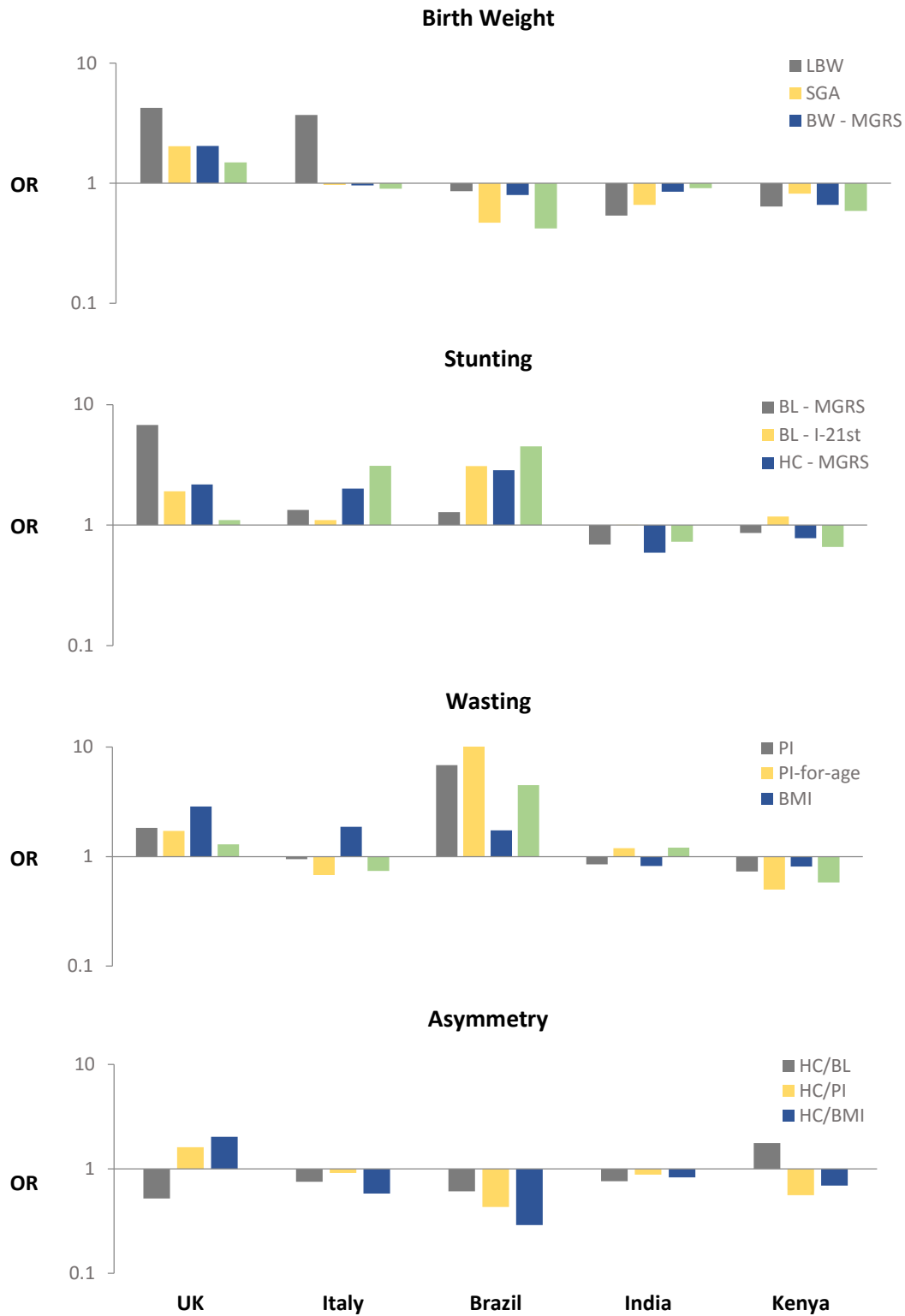


**Figure 6.5 Odds ratios of associations between birth anthropometric indices and attention score across INTERGROWTH-21<sup>st</sup> sites**

Post-hoc analyses of these findings were conducted to confirm whether there were significant associations between stunting indices and attention outcomes in higher-income compared to lower-income sites. As such, the INTERGROWTH-21<sup>st</sup> cohort was divided into two groups for comparison: higher-income countries (UK, Italy and Brazil) and lower-income countries (India and Kenya; Table S6.3). These analyses confirmed stronger associations between all indices of stunting and attention outcomes in higher-income sites (OR range = 1.57-2.15; significant association for HC<10<sup>th</sup> percentile MGRS), compared to lower-income sites (OR range = 0.77-1.01; no significant associations).

#### **6.3.1.2 Association between birth anthropometric indices and cognitive outcomes**

To assess the unadjusted associations between birth anthropometric indices and cognitive outcomes, OLR analyses were conducted separately for the INTERGROWTH-21<sup>st</sup> sites. There were some differences identified in associations between sites (Table 6.6; Table 6.7). Overall, significant associations were identified only in middle- and low-income countries (Brazil, India and Kenya), with no associations identified in the high-income countries (UK and Italy). In Brazil, a significant association was identified between HC<10<sup>th</sup> percentile MGRS and poorer cognitive outcome. In Kenya, a significant association was identified between BW<10<sup>th</sup> percentile MGRS and poorer cognitive outcome. In India, there were a large number of associations identified, particularly in wasting indices. In the Indian INTERGROWTH-21<sup>st</sup> site, BW<10<sup>th</sup> percentile I-21<sup>st</sup>, PI<10<sup>th</sup> percentile, PI-for-age<10<sup>th</sup> percentile, BMI<10<sup>th</sup> percentile and BMI-for-age<10<sup>th</sup> percentile were all associated with poorer cognitive outcomes.

**Table 6.6. Unadjusted associations between birth growth indices and lower cognitive score in childhood in UK, Italy and Brazil**

| Variables                                | UK               |          | Italy            |          | Brazil                   |              |
|------------------------------------------|------------------|----------|------------------|----------|--------------------------|--------------|
|                                          | OR (95%CI)       | <i>p</i> | OR (95%CI)       | <i>p</i> | OR (95%CI)               | <i>p</i>     |
| <b>Birth weight indices</b>              |                  |          |                  |          |                          |              |
| BW <2500g                                | 0.69 (0.17-2.84) | .607     | 0.82 (0.20-3.27) | .773     | 0.80 (0.14-4.39)         | .793         |
| SGA                                      | 0.70 (0.26-1.90) | .487     | 0.82 (0.40-1.67) | .585     | 0.45 (0.17-1.22)         | .117         |
| BW <10 <sup>th</sup> MGRS                | 0.58 (0.22-1.57) | .286     | 0.98 (0.34-1.77) | .540     | 0.82 (0.28-2.41)         | .717         |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.76 (0.49-6.37) | .389     | 0.79 (0.33-1.90) | .600     | 0.54 (0.14-2.12)         | .379         |
| <b>Stunting indices</b>                  |                  |          |                  |          |                          |              |
| BL < 10 <sup>th</sup> MGRS               | 0.46 (0.13-1.58) | .215     | 0.56 (0.22-1.41) | .217     | 1.03 (0.43-2.46)         | .942         |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.78 (0.20-3.05) | .784     | 0.87 (0.31-2.42) | .790     | 0.54 (0.18-1.58)         | .259         |
| HC <10 <sup>th</sup> MGRS                | 0.71 (0.25-2.08) | .538     | 0.61 (0.22-1.74) | .358     | <b>5.22 (1.58-17.28)</b> | <b>.007*</b> |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.42 (0.36-5.59) | .620     | 0.75 (0.12-4.71) | .755     | 2.74 (0.46-16.33)        | .268         |
| <b>Wasting indices</b>                   |                  |          |                  |          |                          |              |
| PI <10 <sup>th</sup> percentile          | 0.51 (0.12-2.20) | .362     | 2.84 (0.95-8.46) | .061     | 3.88 (0.19-80.25)        | .381         |
| PI-for-age <10 <sup>th</sup> percentile  | 1.55 (0.44-5.52) | .497     | 1.70 (0.62-4.64) | .304     | 2.74 (0.31-24.05)        | .362         |
| BMI <10 <sup>th</sup> percentile         | 0.64 (0.10-4.21) | .646     | 2.84 (0.95-8.44) | .061     | 1.54 (0.28-8.55)         | .620         |
| BMI-for-age <10 <sup>th</sup> percentile | 1.10 (0.28-4.37) | .895     | 1.12 (0.42-2.93) | .826     | 2.84 (0.48-16.93)        | .251         |
| <b>Asymmetry indices</b>                 |                  |          |                  |          |                          |              |
| HC/BL >90 <sup>th</sup> percentile       | 2.39 (0.79-7.22) | .121     | 0.76 (0.32-1.76) | .516     | 0.45 (0.18-1.14)         | .093         |
| HC/PI >90 <sup>th</sup> percentile       | 1.18 (0.31-4.46) | .804     | 2.56 (0.93-7.05) | .070     | 2.74 (0.23-32.66)        | .425         |
| HC/BMI >90 <sup>th</sup> percentile      | 1.21 (0.22-6.72) | .828     | 2.78 (0.99-7.78) | .051     | 0.21 (0.02-2.67)         | .229         |

**Table 6.7. Unadjusted associations between birth growth indices and lower cognitive score in childhood in India and Kenya**

| Variables                                | India                   |              | Kenya                   |              |
|------------------------------------------|-------------------------|--------------|-------------------------|--------------|
|                                          | OR (95%CI)              | <i>p</i>     | OR (95%CI)              | <i>p</i>     |
| <b>Birth weight indices</b>              |                         |              |                         |              |
| BW <2500g                                | 1.25 (0.59-2.64)        | .567         | 0.43 (0.18-1.02)        | .054         |
| SGA                                      | 1.17 (0.74-1.87)        | .500         | 0.87 (0.52-1.45)        | .583         |
| BW <10 <sup>th</sup> MGRS                | 1.50 (0.94-2.40)        | .091         | <b>0.47 (0.25-0.89)</b> | <b>.021*</b> |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | <b>1.84 (1.06-3.20)</b> | <b>.031*</b> | 0.62 (0.32-1.21)        | .165         |
| <b>Stunting indices</b>                  |                         |              |                         |              |
| BL < 10 <sup>th</sup> MGRS               | 0.75 (0.43-1.31)        | .314         | 0.75 (0.41-1.35)        | .334         |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.34 (0.66-2.72)        | .415         | 0.85 (0.47-1.52)        | .576         |
| HC <10 <sup>th</sup> MGRS                | 1.20 (0.73-1.99)        | .469         | 0.56 (0.26-1.23)        | .148         |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.29 (0.68-2.44)        | .437         | 0.49 (0.19-1.27)        | .141         |
| <b>Wasting indices</b>                   |                         |              |                         |              |
| PI <10 <sup>th</sup> percentile          | <b>2.11 (1.21-3.67)</b> | <b>.008*</b> | 0.48 (0.22-1.05)        | .064         |
| PI-for-age <10 <sup>th</sup> percentile  | <b>1.91 (1.10-3.13)</b> | <b>.022*</b> | 0.61 (0.27-1.39)        | .240         |
| BMI <10 <sup>th</sup> percentile         | <b>2.10 (1.20-3.67)</b> | <b>.009*</b> | 0.70 (0.33-1.47)        | .345         |
| BMI-for-age <10 <sup>th</sup> percentile | <b>1.81 (1.03-3.18)</b> | <b>.040*</b> | 0.64 (0.31-1.32)        | .229         |
| <b>Asymmetry indices</b>                 |                         |              |                         |              |
| HC/BL >90 <sup>th</sup> percentile       | 0.86 (0.24-3.11)        | .812         | 1.16 (0.65-2.05)        | .622         |
| HC/PI >90 <sup>th</sup> percentile       | 1.64 (0.91-2.96)        | .102         | 0.91 (0.47-1.79))       | .791         |
| HC/BMI >90 <sup>th</sup> percentile      | 1.65 (0.91-2.97)        | .097         | 0.51 (0.25-1.04)        | .064         |

The pattern of ORs was examined to identify differences in the associations between birth anthropometric indices and cognitive outcomes across site (Figure 6.6). These results, however, must be interpreted with caution as there were not birth anthropometric index\*site interactions identified (with the exception of BL<10<sup>th</sup> percentile MGRS). Some difference between sites were identified in the associations between wasting indices and cognitive outcome, whereby wasting was positively associated with poor cognitive outcomes in Italy, Brazil and India, but negatively associated in Kenya (with mixed results in the UK). There were no clear differences in the other anthropometric indices (BW, stunting or asymmetry).

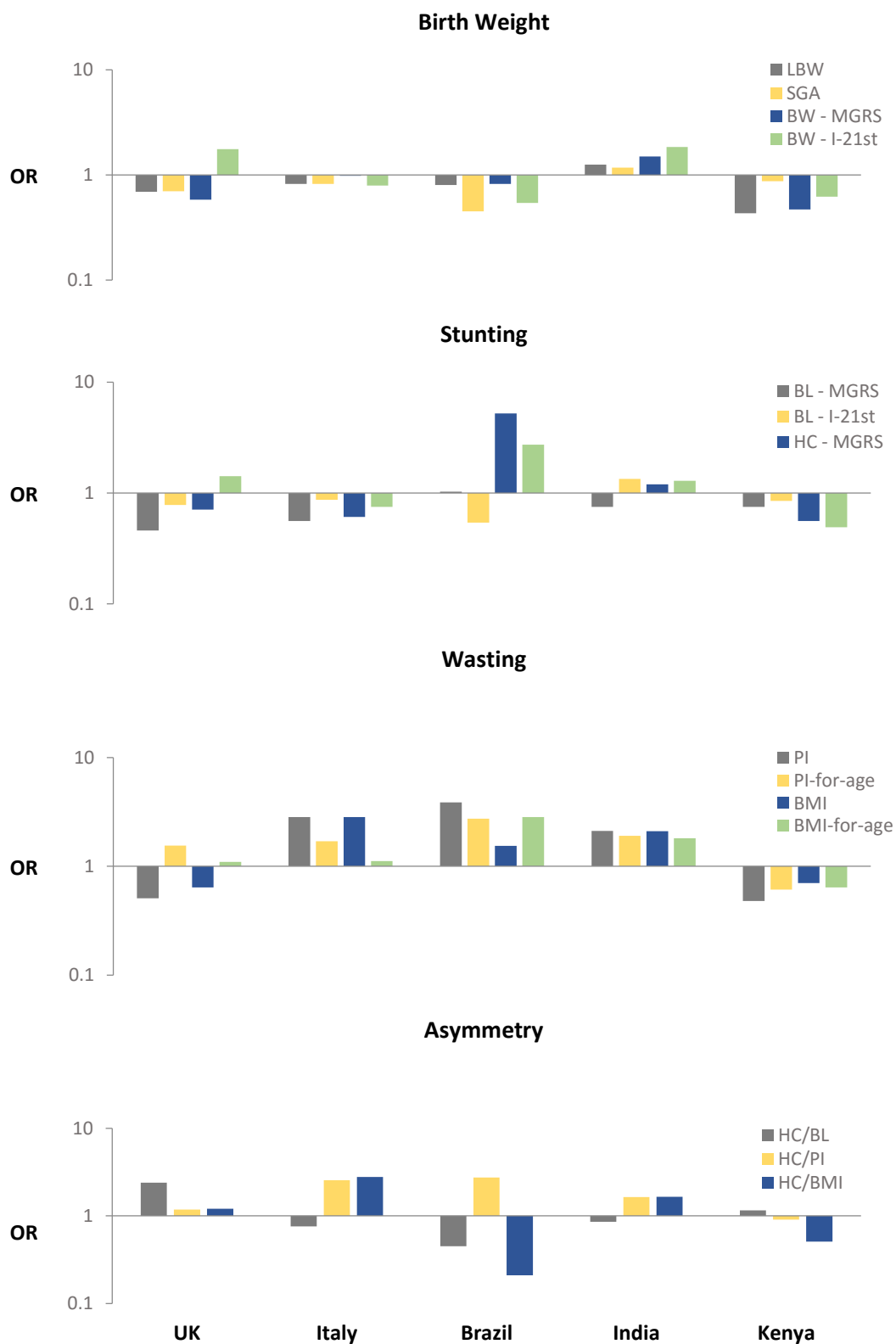


Figure 6.6. Odds ratios of associations between birth anthropometric indices and cognitive score across INTERGROWTH-21<sup>st</sup> sites

Finally, differences in sensitivity and specificity were examined across INTERGROWTH-21<sup>st</sup> sites to determine whether there may be cross-site differences in the predictive value of birth indices for attention impairment (Tables S6.4-S6.8) and cognitive impairment (Tables S6.8-S6.12). The results across site were consistent for attention outcomes, with stunting identified as a stronger predictor of attention impairment than any of the other birth anthropometric indices. For cognitive outcomes, different indices were identified as the strongest predictors of cognitive impairment across all sites: UK (HC/BL), Italy (HC/PI), Brazil (HC/PI), Kenya (HC/BMI), and India (BMI-for-age).

### **6.3.2 Study II: Comparison between descriptive and low-risk cohorts from the same location**

For the UK comparison, data was available on 168 children from the INTERGROWTH-21<sup>st</sup> UK site for both attention and cognitive outcomes, and from 7829 children from the ALSPAC cohort for attention outcomes and a subsample of 1010 children for cognitive outcomes. For the Brazil comparison, data was available on 108 children from the INTERGROWTH-21<sup>st</sup> Brazil site for both attention and cognitive outcomes, and from 3749 children from the 2004 Pelotas birth cohort for attention outcomes and 3395 children for cognitive outcomes.

Differences in maternal and child characteristics between the INTERGROWTH-21<sup>st</sup> UK site and the ALSPAC cohort, and between the INTERGROWTH-21<sup>st</sup> Brazil site and the Pelotas 2004 birth cohort are presented in Table S6.14. In the UK comparison, the INTERGROWTH-21<sup>st</sup> mothers had significantly more years of schooling (16.26 compared to 10.79 years), were older at delivery (30.59 compared to 27.96 years), had a higher prevalence of caesarean section (16.15% compared to 9.9%) and had a lower prevalence of breastfeeding <6 months (31.6% compared to 64.5%). For the Brazil comparison, INTERGROWTH-21<sup>st</sup> mothers had significantly more years of schooling (13.86 compared to 8.13 years), were older at delivery (28.75 compared



to 26.19 years), had a higher prevalence of caesarean section (85.8% compared to 45.5%), and a lower prevalence of breastfeeding <6 months (24.8% compared to 49.6%).

Differences in the prevalence of birth anthropometric indices between the INTERGROWTH-21<sup>st</sup> UK site and the ALSPAC cohort, and between the INTERGROWTH-21<sup>st</sup> Brazil site and the Pelotas 2004 birth cohort are presented in Table 6.8. In the UK comparison, the INTERGROWTH-21<sup>st</sup> cohort had a higher prevalence of HC<10<sup>th</sup> percentile according to INTERGROWTH-21<sup>st</sup> standards (5.3% compared to 2.8%), but a lower prevalence of wasting and asymmetry indices. In the Brazil comparison, the INTERGROWTH-21<sup>st</sup> cohort had a lower prevalence of BL<10<sup>th</sup> percentile according to I-21<sup>st</sup> standards (10.6% compared to 18.8%), HC<10<sup>th</sup> percentile according to MGRS standards (8.8% compared to 16.2%), and wasting indices, but a higher prevalence of asymmetry indices.

**Table 6.8. Frequency n(%) and chi-squared analyses of birth indices by INTERGROWTH-21st site and Pelotas and ALSPAC cohorts**

| Variable                                 | I-21 <sup>st</sup> UK<br>(N=168) | ALSPAC<br>(N=13445) | $\chi^2$ | <i>p</i> | I-21 <sup>st</sup> Brazil<br>(N=108) | Pelotas<br>(N=3749) | $\chi^2$ | <i>p</i> |
|------------------------------------------|----------------------------------|---------------------|----------|----------|--------------------------------------|---------------------|----------|----------|
| <b>Birth weight indices</b>              |                                  |                     |          |          |                                      |                     |          |          |
| BW <2500g                                | 6 (3.4)                          | 589 (4.4)           | 0.36     | .709     | 5 (4.4)                              | 340 (9.1)           | 2.91     | .094     |
| SGA                                      | 13 (7.5)                         | 1154 (8.5)          | 0.27     | .672     | 15 (13.3)                            | 553 (14.8)          | 0.19     | .787     |
| BW <10 <sup>th</sup> MGRS                | 14 (8.0)                         | 1302 (9.6)          | 0.53     | .597     | 13 (11.5)                            | 694 (18.5)          | 3.61     | .063     |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 7 (4.0)                          | 773 (5.7)           | 0.95     | .412     | 8 (7.1)                              | 361 (9.6)           | 0.82     | .514     |
| <b>Stunting indices</b>                  |                                  |                     |          |          |                                      |                     |          |          |
| BL <10 <sup>th</sup> MGRS                | 9 (5.3)                          | 640 (6.2)           | 0.28     | .749     | 23 (20.4)                            | 1057 (28.3)         | 3.44     | .071     |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 9 (5.3)                          | 413 (4.0)           | 0.66     | .429     | 12 (10.6)                            | 700 (18.8)          | 4.83     | .027*    |
| HC <10 <sup>th</sup> MGRS                | 14 (8.1)                         | 561 (5.4)           | 2.41     | .126     | 10 (8.8)                             | 606 (16.2)          | 4.44     | .036*    |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 10 (5.8)                         | 242 (2.3)           | 8.72     | .008*    | 3 (2.7)                              | 276 (7.4)           | 3.67     | .063     |
| <b>Wasting indices</b>                   |                                  |                     |          |          |                                      |                     |          |          |
| PI <10 <sup>th</sup> percentile          | 5 (2.9)                          | 1013 (10.0)         | 9.44     | .002*    | 1 (0.9)                              | 374 (10.0)          | 10.40    | <.001**  |
| PI-for-age <10 <sup>th</sup> percentile  | 8 (4.7)                          | 1009 (10.0)         | 5.26     | .025*    | 2 (1.8)                              | 363 (9.7)           | 8.09     | .002*    |
| BMI <10 <sup>th</sup> percentile         | 3 (1.8)                          | 1014 (10.0)         | 12.86    | <.001**  | 4 (3.5)                              | 372 (10.0)          | 5.14     | .023*    |
| BMI-for-age <10 <sup>th</sup> percentile | 6 (3.5)                          | 1008 (9.9)          | 7.84     | .005*    | 3 (2.7)                              | 364 (9.8)           | 6.41     | .008*    |
| <b>Asymmetry indices</b>                 |                                  |                     |          |          |                                      |                     |          |          |
| HC/BL >90 <sup>th</sup> percentile       | 12 (7.0)                         | 1024 (9.7)          | 1.66     | .248     | 21 (18.6)                            | 370 (9.9)           | 9.02     | .006*    |
| HC/PI >90 <sup>th</sup> percentile       | 7 (4.1)                          | 1013 (10.0)         | 6.57     | .010*    | 2 (1.8)                              | 373 (9.9)           | 8.43     | .001*    |
| HC/BMI >90 <sup>th</sup> percentile      | 4 (2.3)                          | 1012 (10.0)         | 11.07    | .001*    | 3 (2.7)                              | 373 (9.9)           | 6.70     | .006*    |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21st = INTERGROWTH-21st growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

Differences in the prevalence of poor attention and cognitive outcomes as a dichotomous variable between the INTERGROWTH-21<sup>st</sup> UK site and the ALSPAC cohort, and between the INTERGROWTH-21<sup>st</sup> Brazil site and the Pelotas 2004 birth cohort are presented in Table 6.9. No differences were identified between cohorts, with the exception of a lower prevalence of poor attention outcomes in the INTERGROWTH-21<sup>st</sup> UK cohort (4.1%), compared to ALSPAC (11.0%).

**Table 6.9. Frequency n(%) and chi-squared analyses of attention and cognitive impairment by site**

| Variable                            | Attention   | Cognitive   |
|-------------------------------------|-------------|-------------|
| INTERGROWTH-21 <sup>st</sup> UK     | 6 (4.1%)    | 34 (20.1%)  |
| ALSPAC                              | 858 (11.0%) | 154 (15.5%) |
| $\chi^2$                            | 6.96        | 2.36        |
| <i>p</i>                            | .007*       | .125        |
| INTERGROWTH-21 <sup>st</sup> Brazil | 4 (3.5%)    | 16 (14.2%)  |
| Pelotas 2004 Birth Cohort           | 273 (7.3%)  | 623 (16.6)  |
| $\chi^2$                            | 2.31        | 0.48        |
| <i>p</i>                            | .191        | .607        |

Impairments = SDQ score  $\geq 7$ ; CBCL *t* score  $\geq 67$ ; INTER-NDA score  $>1SD$  below mean \* =  $p < .05$ ; \*\* =  $p < .001$

### 6.3.2.1 Association between birth anthropometric indices and attention and cognitive outcomes in the UK

Associations between birth anthropometric indices and attention and cognitive outcomes were compared between the INTERGROWTH-21<sup>st</sup> UK sample and the ALSPAC cohort. For attention outcomes, significant associations were identified in both ALSPAC and the INTERGROWTH-21<sup>st</sup> UK sample with BL<10<sup>th</sup> percentile by MGRS standards. Significant associations were identified with BW indices (SGA and BW<10<sup>th</sup> percentile by MGRS standards) and attention outcomes in ALSPAC only (Table 6.10). The pattern of association for attention outcomes was consistent between cohorts for all birth indices (BW, stunting, wasting and asymmetry; Figure 6.7).

**Table 6.10. Associations between birth anthropometric indices and high attention score in childhood in ALSPAC and INTERGROWTH-21st UK**

| Variables                                | ALSPAC      |                  |              | INTERGROWTH-21 <sup>st</sup> UK |                   |              |
|------------------------------------------|-------------|------------------|--------------|---------------------------------|-------------------|--------------|
|                                          | OR          | 95%CI            | p            | OR                              | 95%CI             | p            |
| <b>Birth weight indices</b>              |             |                  |              |                                 |                   |              |
| BW <2500g                                | 2.12        | 0.82-0.49        | .122         | 4.26                            | 0.69-26.32        | .119         |
| SGA                                      | <b>1.84</b> | <b>1.01-3.34</b> | <b>.046*</b> | 2.04                            | 0.64-6.52         | .231         |
| BW <10 <sup>th</sup> MGRS                | <b>2.11</b> | <b>1.13-3.95</b> | <b>.020*</b> | 2.05                            | 0.64-6.54         | .225         |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.41        | 0.69-2.85        | .346         | 1.49                            | 0.34-6.53         | .599         |
| <b>Stunting indices</b>                  |             |                  |              |                                 |                   |              |
| BL < 10 <sup>th</sup> MGRS               | <b>2.84</b> | <b>1.42-5.69</b> | <b>.003*</b> | <b>6.78</b>                     | <b>1.50-30.59</b> | <b>.013*</b> |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.13        | 0.90-5.03        | .085         | 1.91                            | 0.45-8.15         | .384         |
| HC <10 <sup>th</sup> MGRS                | 1.94        | 0.78-4.81        | .155         | 2.17                            | 0.63-7.47         | .218         |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.75        | 0.26-2.16        | .595         | 1.10                            | 0.28-4.39         | .891         |
| <b>Wasting indices</b>                   |             |                  |              |                                 |                   |              |
| PI <10 <sup>th</sup> percentile          | 1.03        | 0.59-1.78        | .925         | 1.83                            | 0.28-12.02        | .531         |
| PI-for-age <10 <sup>th</sup> percentile  | 1.15        | 0.68-1.96        | .602         | 1.72                            | 0.47-6.30         | .411         |
| BMI <10 <sup>th</sup> percentile         | 1.62        | 0.93-2.84        | .088         | 2.86                            | 0.31-26.50        | .355         |
| BMI-for-age <10 <sup>th</sup> percentile | 1.29        | 0.75-2.21        | .361         | 1.29                            | 0.27-6.08         | .750         |
| <b>Asymmetry indices</b>                 |             |                  |              |                                 |                   |              |
| HC/BL >90 <sup>th</sup> percentile       | 1.54        | 0.87-2.74        | .142         | 0.52                            | 0.15-1.7)         | .289         |
| HC/PI >90 <sup>th</sup> percentile       | 1.06        | 0.61-1.85        | .828         | 1.61                            | 0.40-6.45         | .505         |
| HC/BMI >90 <sup>th</sup> percentile      | 1.57        | 0.89-2.78        | .120         | 2.03                            | 0.34-12.33        | .440         |

ALSPAC fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; INTERGROWTH-21<sup>st</sup> UK unadjusted model; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

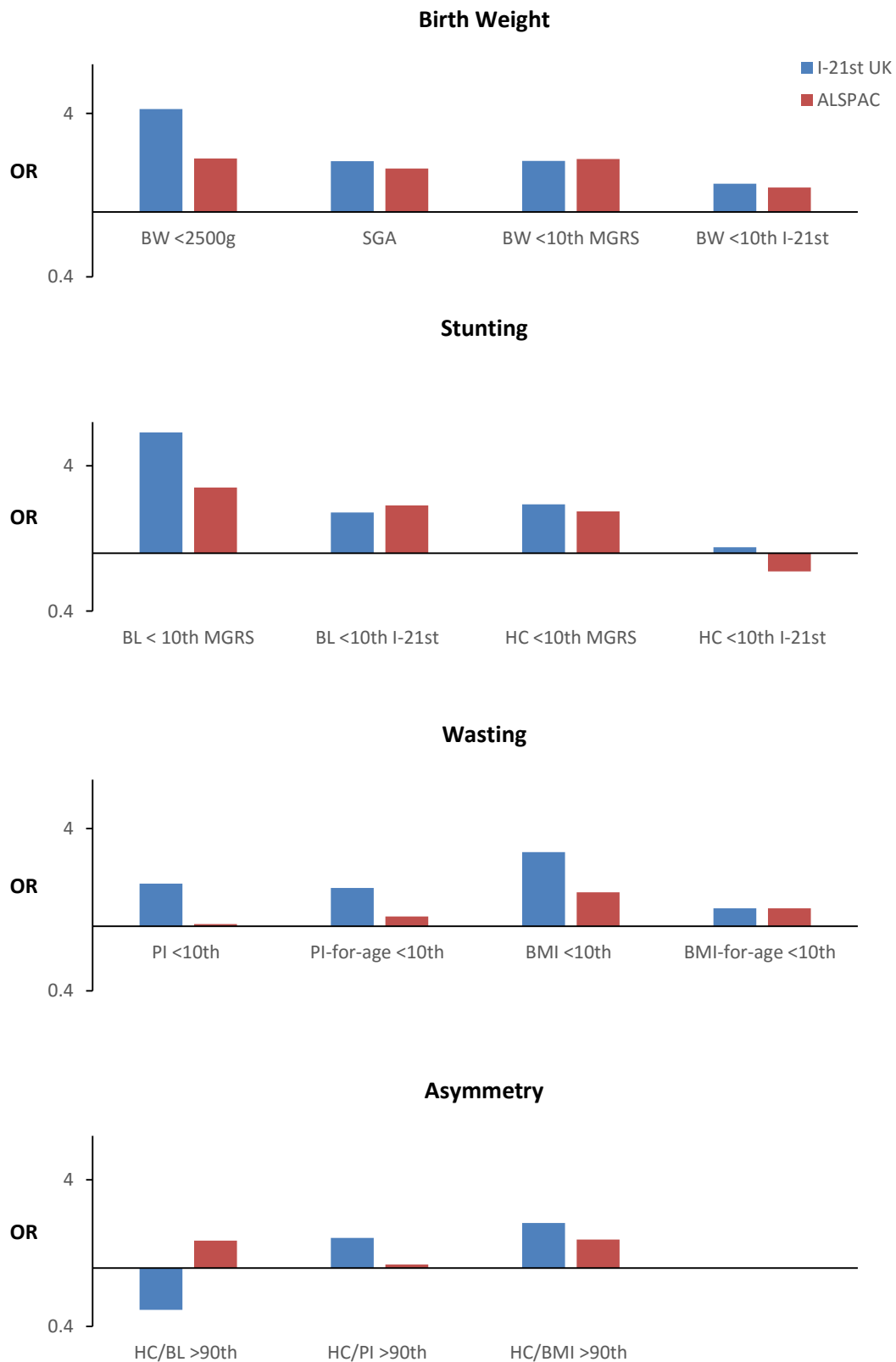


**Figure 6.7. Associations (ORs) between birth anthropometric indices and poor attention outcomes in childhood in ALSPAC and INTERGROWTH-21<sup>st</sup> UK**

Associations between birth anthropometric indices and cognitive outcomes were also compared between the INTERGROWTH-21<sup>st</sup> UK sample and the ALSPAC cohort (Table 6.11). A significant association was identified in ALSPAC between BW<10<sup>th</sup> percentile by MGRS standards and cognitive outcomes. There were no significant associations identified between birth anthropometric indices and cognitive outcomes in the INTERGROWTH-21<sup>st</sup> UK cohort. There were some differences between cohorts in the pattern of associations for cognitive outcomes, predominantly in indices of BW and stunting (Figure 6.8).

**Table 6.11. Associations between birth anthropometric indices and low cognitive score in childhood in ALSPAC and INTERGROWTH-21st UK**

| Variables                                | ALSPAC      |                  |              | INTERGROWTH-21 <sup>st</sup> UK |           |      |
|------------------------------------------|-------------|------------------|--------------|---------------------------------|-----------|------|
|                                          | OR          | 95%CI            | p            | OR                              | 95%CI     | p    |
| <b>Birth weight indices</b>              |             |                  |              |                                 |           |      |
| BW <2500g                                | 2.22        | 0.51-9.71        | .288         | 0.69                            | 0.17-2.84 | .607 |
| SGA                                      | 0.86        | 0.33-2.25        | .752         | 0.70                            | 0.26-1.90 | .487 |
| BW <10 <sup>th</sup> MGRS                | <b>2.48</b> | <b>1.30-4.73</b> | <b>.006*</b> | 0.58                            | 0.22-1.57 | .286 |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.50        | 0.42-5.39        | .539         | 1.76                            | 0.49-6.37 | .389 |
| <b>Stunting indices</b>                  |             |                  |              |                                 |           |      |
| BL < 10 <sup>th</sup> MGRS               | 1.77        | 0.86-3.64        | .121         | 0.46                            | 0.13-1.58 | .215 |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.60        | 0.58-4.46        | .368         | 0.78                            | 0.20-3.05 | .784 |
| HC <10 <sup>th</sup> MGRS                | 1.12        | 0.30-4.22        | .869         | 0.71                            | 0.25-2.08 | .538 |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.10        | 0.25-4.90        | .899         | 1.42                            | 0.36-5.59 | .620 |
| <b>Wasting indices</b>                   |             |                  |              |                                 |           |      |
| PI <10 <sup>th</sup> percentile          | 0.94        | 0.53-1.66        | .822         | 0.51                            | 0.12-2.20 | .362 |
| PI-for-age <10 <sup>th</sup> percentile  | 0.93        | 0.52-1.65        | .812         | 1.55                            | 0.44-5.52 | .497 |
| BMI <10 <sup>th</sup> percentile         | 1.22        | 0.70-2.16        | .483         | 0.64                            | 0.10-4.21 | .646 |
| BMI-for-age <10 <sup>th</sup> percentile | 1.06        | 0.60-1.86        | .840         | 1.10                            | 0.28-4.37 | .895 |
| <b>Asymmetry indices</b>                 |             |                  |              |                                 |           |      |
| HC/BL >90 <sup>th</sup> percentile       | 1.01        | 0.54-1.90        | .979         | 2.39                            | 0.79-7.22 | .121 |
| HC/PI >90 <sup>th</sup> percentile       | 1.04        | 0.61-1.80        | .876         | 1.18                            | 0.31-4.46 | .804 |
| HC/BMI >90 <sup>th</sup> percentile      | 1.01        | 0.56-1.81        | .974         | 1.21                            | 0.22-6.72 | .828 |

ALSPAC fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; INTERGROWTH-21<sup>st</sup> UK unadjusted model; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

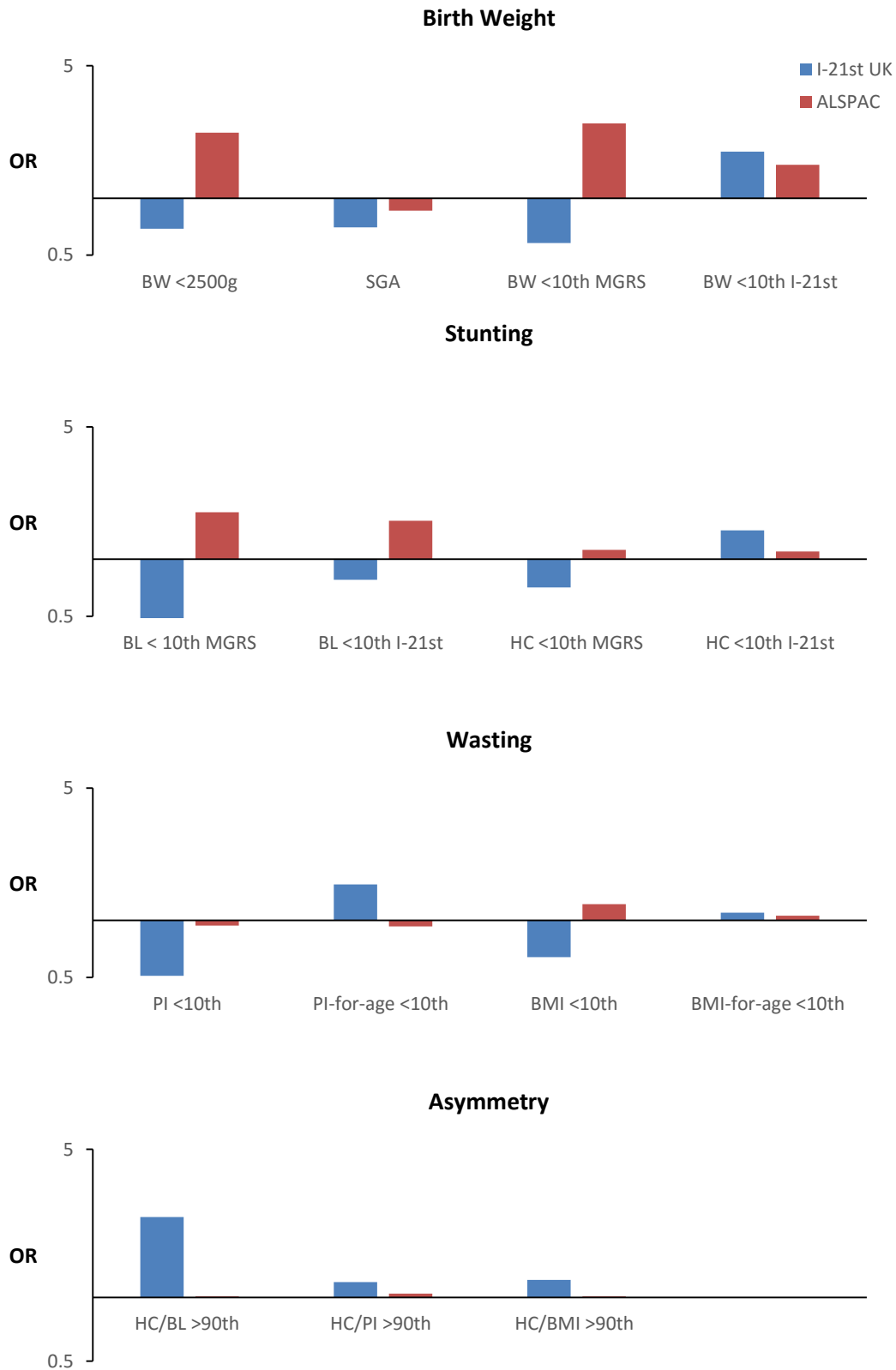


**Figure 6.8. Associations (ORs) between birth anthropometric indices and poor cognitive outcomes in childhood in ALSPAC and INTERGROWTH-21<sup>st</sup> UK**



### **6.3.2.2 Association between birth anthropometric indices and attention and cognitive outcomes in Brazil**

Associations between birth anthropometric indices and attention and cognitive outcomes were compared between the INTERGROWTH-21<sup>st</sup> Brazil sample and the Pelotas 2004 birth cohort. For attention outcomes, significant associations were identified in both the INTERGROWTH-21<sup>st</sup> Brazil sample and the Pelotas 2004 birth cohort in BL<10<sup>th</sup> percentile by INTERGROWTH-21<sup>st</sup> standards. Significant associations were identified in the INTERGROWTH-21<sup>st</sup> Brazil sample only with PI-for-age<10<sup>th</sup> percentile, and in the Pelotas cohort only with BW indices (SGA and BW<10<sup>th</sup> percentile by MGRS standards) and stunting indices (BL and HC<10<sup>th</sup> percentile by MGRS standards). The pattern of associations for attention outcomes were consistent between cohorts for stunting and wasting indices, but differed for BW and asymmetry indices (Figure 6.9).

**Table 6.12. Associations between birth anthropometric indices and higher attention score in childhood in Pelotas 2004 birth cohort and INTERGROWTH-21st Brazil**

| Variables                                | Pelotas 2004 |                  |              | INTERGROWTH-21 <sup>st</sup> Brazil |                    |              |
|------------------------------------------|--------------|------------------|--------------|-------------------------------------|--------------------|--------------|
|                                          | OR           | 95%CI            | <i>p</i>     | OR                                  | 95%CI              | <i>p</i>     |
| <b>Birth weight indices</b>              |              |                  |              |                                     |                    |              |
| BW <2500g                                | 1.15         | 0.90-1.47        | .255         | 0.86                                | 0.15-5.15          | .872         |
| SGA                                      | <b>1.23</b>  | <b>1.04-1.47</b> | <b>.017*</b> | 0.47                                | 0.19-1.15          | .097         |
| BW <10 <sup>th</sup> MGRS                | <b>1.21</b>  | <b>1.02-1.44</b> | <b>.033*</b> | 0.80                                | 0.29-2.16          | .656         |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | <b>1.38</b>  | <b>1.12-1.70</b> | <b>.003*</b> | 0.42                                | 0.13-1.38          | .154         |
| <b>Stunting indices</b>                  |              |                  |              |                                     |                    |              |
| BL < 10 <sup>th</sup> MGRS               | <b>1.20</b>  | <b>1.04-1.39</b> | <b>.015*</b> | 1.28                                | 0.56-2.91          | .553         |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | <b>1.24</b>  | <b>1.06-1.46</b> | <b>.009*</b> | <b>3.09</b>                         | <b>1.03-9.26</b>   | <b>.044*</b> |
| HC <10 <sup>th</sup> MGRS                | <b>1.37</b>  | <b>1.14-1.64</b> | <b>.001*</b> | 2.86                                | 0.86-9.55          | .086         |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.26         | 1.00-1.58        | .053         | 4.50                                | 0.57-35.42         | .153         |
| <b>Wasting indices</b>                   |              |                  |              |                                     |                    |              |
| PI <10 <sup>th</sup> percentile          | 1.15         | 0.94-1.41        | .189         | 6.84                                | 0.38-124.36        | .194         |
| PI-for-age <10 <sup>th</sup> percentile  | 1.06         | 0.86-1.29        | .603         | <b>12.14</b>                        | <b>1.38-106.43</b> | <b>.024*</b> |
| BMI <10 <sup>th</sup> percentile         | 1.19         | 0.96-1.48        | .122         | 1.74                                | 0.24-12.83         | .588         |
| BMI-for-age <10 <sup>th</sup> percentile | 1.21         | 0.99-1.49        | .063         | 4.49                                | 0.57-35.37         | .154         |
| <b>Asymmetry indices</b>                 |              |                  |              |                                     |                    |              |
| HC/BL >90 <sup>th</sup> percentile       | 1.19         | 0.97-1.46        | .088         | 0.61                                | 0.26-1.46          | .268         |
| HC/PI >90 <sup>th</sup> percentile       | 1.04         | 0.85-1.27        | .711         | 0.43                                | 0.04-3.43          | .475         |
| HC/BMI >90 <sup>th</sup> percentile      | 1.15         | 0.93-1.41        | .193         | 0.29                                | 0.05-1.75          | .178         |

ALSPAC fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; INTERGROWTH-21<sup>st</sup> UK unadjusted model; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* =  $p < .05$ ; \*\*= $p < .001$

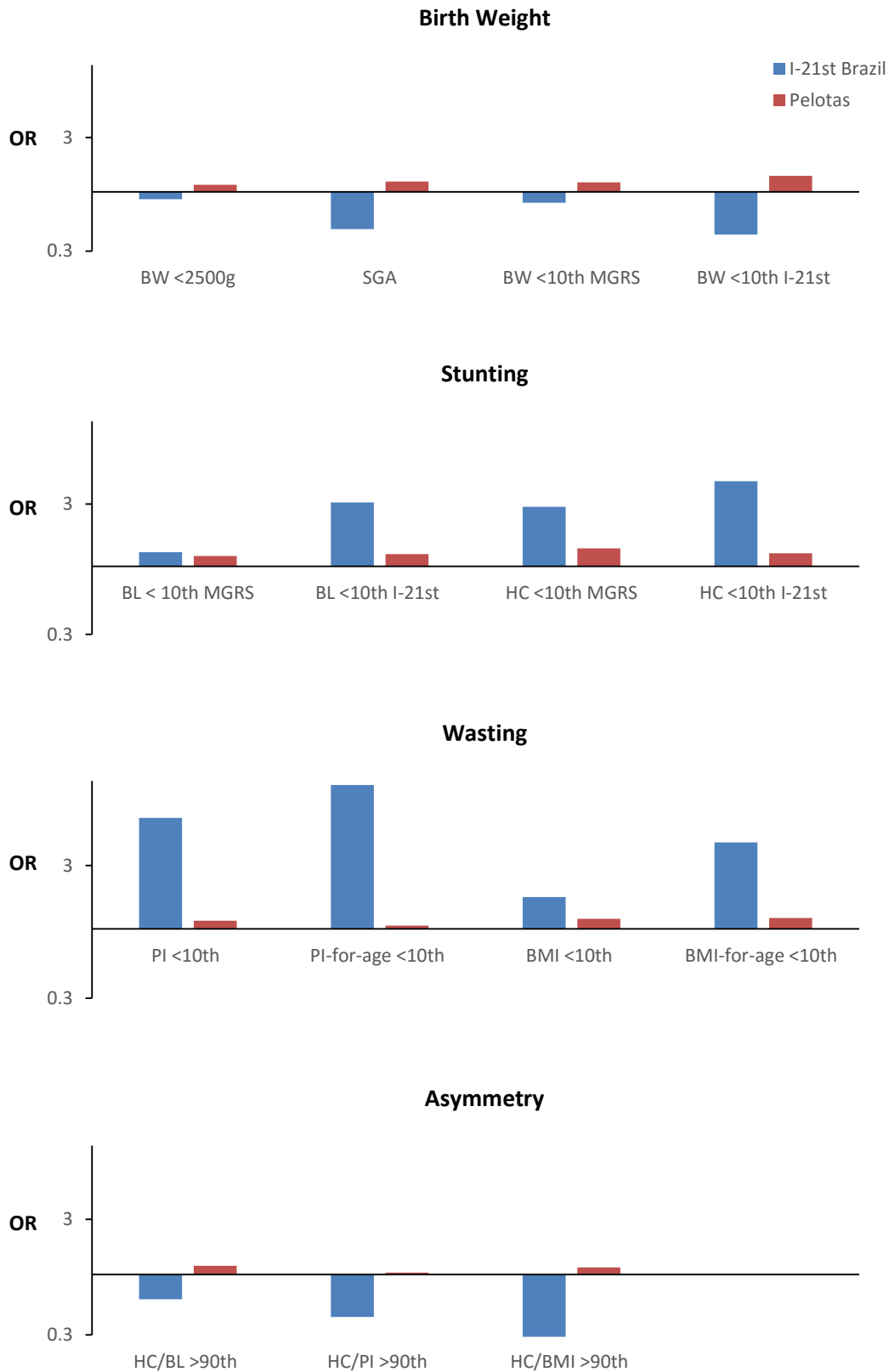


**Figure 6.9. Associations (ORs) between birth anthropometric indices and poor attention outcomes in childhood in Pelotas 2004 birth cohort and INTERGROWTH-21<sup>st</sup> Brazil**

Associations between birth anthropometric indices and cognitive outcomes were also compared between the INTERGROWTH-21<sup>st</sup> Brazil sample and the Pelotas 2004 birth cohort (Table 6.13). There were many significant associations identified in Pelotas 2004 (most BW indices, with the exception of BW<2500g, all stunting indices, some wasting indices (PI<10<sup>th</sup> percentile and BMI<10<sup>th</sup> percentile) and one asymmetry index (HC/BMI>90<sup>th</sup> percentile)). Only one association was identified between birth anthropometric indices and cognitive outcome in the INTERGROWTH-21<sup>st</sup> Brazil sample, with a significant association identified between poor cognitive outcomes and HC<10<sup>th</sup> percentile by MGRS standards only. This, however, may be a function of reduced power due to low sample size in the INTERGROWTH-21<sup>st</sup> Brazil sample. There were some consistencies between cohorts in the pattern (direction) of associations for cognitive outcomes, predominantly in indices of stunting (BL<10<sup>th</sup> percentile MGRS, HC<10<sup>th</sup> percentile MGRS and HC<10<sup>th</sup> percentile I-21<sup>st</sup>) and wasting (all indices; Figure 6.10).

**Table 6.13. Associations between birth anthropometric indices and lower cognitive score in childhood in Pelotas 2004 birth cohort and INTERGROWTH-21st Brazil**

| Variables                                | Pelotas 2004 |                  |                   | INTERGROWTH-21 <sup>st</sup> Brazil |                   |              |
|------------------------------------------|--------------|------------------|-------------------|-------------------------------------|-------------------|--------------|
|                                          | OR           | 95%CI            | p                 | OR                                  | 95%CI             | p            |
| <b>Birth weight indices</b>              |              |                  |                   |                                     |                   |              |
| BW <2500g                                | 1.21         | 0.94-1.55        | .138              | 0.80                                | 0.14-4.39         | .793         |
| SGA                                      | <b>1.27</b>  | <b>1.07-1.52</b> | <b>.008*</b>      | 0.45                                | 0.17-1.22         | .117         |
| BW <10 <sup>th</sup> MGRS                | <b>1.20</b>  | <b>1.00-1.44</b> | <b>.047*</b>      | 0.82                                | 0.28-2.41         | .717         |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | <b>1.34</b>  | <b>1.08-1.67</b> | <b>.008*</b>      | 0.54                                | 0.14-2.12         | .379         |
| <b>Stunting indices</b>                  |              |                  |                   |                                     |                   |              |
| BL < 10 <sup>th</sup> MGRS               | <b>1.18</b>  | <b>1.02-1.38</b> | <b>.032*</b>      | 1.03                                | 0.43-2.46         | .942         |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | <b>1.30</b>  | <b>1.10-1.54</b> | <b>.002*</b>      | 0.54                                | 0.18-1.58         | .259         |
| HC <10 <sup>th</sup> MGRS                | <b>1.42</b>  | <b>1.17-1.71</b> | <b>&lt;.001**</b> | <b>5.22</b>                         | <b>1.58-17.28</b> | <b>.007*</b> |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | <b>1.53</b>  | <b>1.20-1.95</b> | <b>.001*</b>      | 2.74                                | 0.46-16.33        | .268         |
| <b>Wasting indices</b>                   |              |                  |                   |                                     |                   |              |
| PI <10 <sup>th</sup> percentile          | <b>1.33</b>  | <b>1.08-1.64</b> | <b>.008*</b>      | 3.88                                | 0.19-80.25        | .381         |
| PI-for-age <10 <sup>th</sup> percentile  | 1.12         | 0.91-1.39        | .284              | 2.74                                | 0.31-24.05        | .362         |
| BMI <10 <sup>th</sup> percentile         | <b>1.37</b>  | <b>1.09-1.72</b> | <b>.006*</b>      | 1.54                                | 0.28-8.55         | .620         |
| BMI-for-age <10 <sup>th</sup> percentile | 1.15         | 0.93-1.42        | .202              | 2.84                                | 0.48-16.93        | .251         |
| <b>Asymmetry indices</b>                 |              |                  |                   |                                     |                   |              |
| HC/BL >90 <sup>th</sup> percentile       | 1.20         | 0.97-1.49        | .101              | 0.45                                | 0.18-1.14         | .093         |
| HC/PI >90 <sup>th</sup> percentile       | 1.10         | 0.89-1.35        | .387              | 2.74                                | 0.23-32.66        | .425         |
| HC/BMI >90 <sup>th</sup> percentile      | <b>1.34</b>  | <b>1.08-1.67</b> | <b>.008*</b>      | 0.21                                | 0.02-2.67         | .229         |

ALSPAC fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; INTERGROWTH-21<sup>st</sup> UK unadjusted model; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

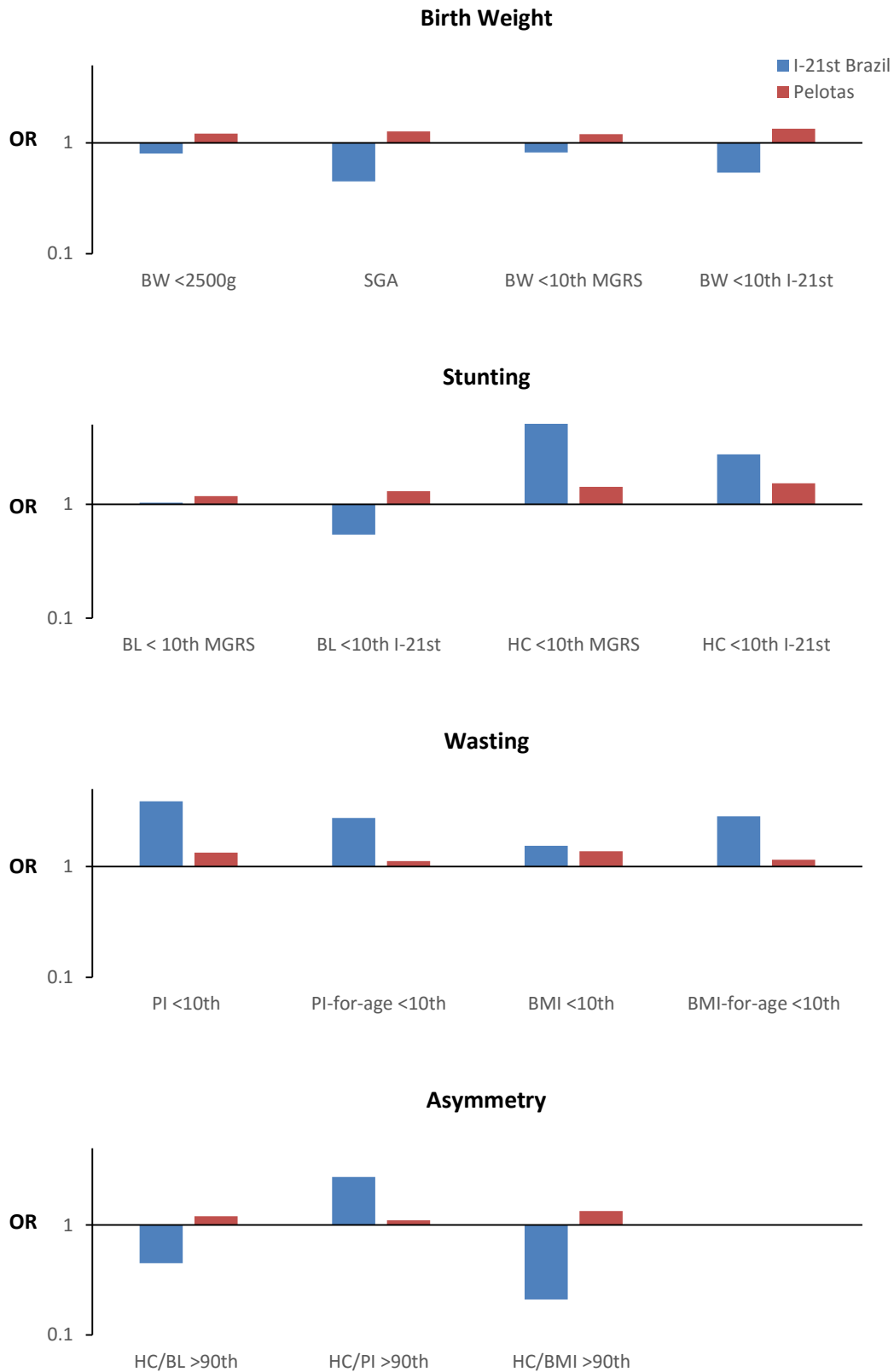


**Figure 6.10. Associations (ORs) between birth anthropometric indices and poor cognitive outcomes in childhood in Pelotas 2004 birth cohort and INTERGROWTH-21<sup>st</sup> Brazil**

## **6.4 Summary of results**

The aim of this chapter was to examine whether the association between birth anthropometric indices and attention and cognitive development differs between high-, middle- and low-income countries by examining 1) variability between INTERGROWTH-21<sup>st</sup> sites, and 2) variability between descriptive and low-risk cohorts within the same geographical location. Based on previous research, it was hypothesised in Study I that associations in LMICs would be stronger than in HICs. This was supported for cognitive outcomes, but not for attention outcomes. The second hypothesis (Study II) was that there would be more associations in descriptive compared to low-risk samples, which was supported by the findings. The specific findings of each study are summarised below.

### **6.4.1 Summary of Study I**

Study I identified variation in associations between stunting indices and attention outcomes across sites, whereby stunting was positively associated with poor attention outcomes in the UK, Italy and Brazil, but not in India and Kenya. For cognitive outcomes, associations were only identified in middle- and low-income countries (Brazil, India and Kenya), with indices of stunting and wasting. There was variation across these sites, however, for which birth anthropometric index was the strongest predictor of poor cognitive outcomes. No associations between birth anthropometric indices and cognitive outcomes were identified in high-income countries (UK and Italy).

### **6.4.2 Summary of Study II**

Study II identified similar patterns of associations between birth anthropometric indices and attention and cognitive outcomes between descriptive and low-risk cohorts in the same site, although more associations were identified in descriptive cohorts (ALSPAC and Pelotas 2004 birth cohort) than in the low-risk cohorts (INTERGROWTH-21<sup>st</sup> UK and Brazil sites). This suggests that in low-risk mothers, there is less likelihood that fetal growth impairment will be associated

with poor attention and cognitive outcomes. This may indicate that maternal 'low-risk' status provides some level of protection against the poor outcomes associated with impaired fetal growth. The finding of *some* associations, however, suggests that low-risk mothers are not entirely protected from poor outcomes associated with impaired fetal growth.

### **6.4.3 How this chapter builds on previous chapters**

The results of the current chapter provide further explanation for the results of Chapter 5. Chapter 5 showed no associations between any birth anthropometric indices and attention and cognitive outcomes in the INTERGROWTH-21<sup>st</sup> cohort. The findings of the current chapter suggest that a possible reason for this may be that the associations may not have been immediately identifiable in the INTERGROWTH-21<sup>st</sup> study when all sites were pooled, due to differences in the associations between higher- and lower-income countries. When disaggregated across INTERGROWTH-21<sup>st</sup> site, the results of the current chapter provide support for the findings of Chapter 5 in two main ways.

Firstly, Chapter 5 identified an association between stunting and attention outcomes in the ALSPAC and Pelotas cohorts, but not in the INTERGROWTH-21<sup>st</sup> cohort (all sites pooled). When the INTERGROWTH-21<sup>st</sup> sites were disaggregated in Study I of the current chapter, the results showed associations of stunting and attention outcomes between the higher-income countries (UK, Italy and Brazil), but not the lower income countries (India and Kenya).

Secondly, for cognitive outcomes, Chapter 5 showed associations across a number of different birth anthropometric indices in Pelotas, but not in ALSPAC or INTERGROWTH-21<sup>st</sup>. The results of Study I of the current chapter support this finding, showing associations between a number of birth anthropometric indices and poor cognitive outcomes in middle- and low-income samples (Brazil, India and Kenya), but not in the high-income samples (UK and Italy).

Finally, the results of Study II of the current chapters suggest that there may be fewer associations identifiable in low-risk samples, compared to descriptive samples. This may suggest



some partial protection associated with maternal low-risk status. This may further explain the results of Chapter 5, which identified significantly fewer associations in the INTERGROWTH-21<sup>st</sup> cohort, compared to the Pelotas and ALSPAC cohorts.

## **6.5 Conclusions**

The findings of this chapter suggest that there were some differences between INTERGROWTH-21<sup>st</sup> sites in the associations between birth anthropometric indices and attention and cognitive outcomes. Differences in associations were identified between the higher-income and lower-income countries for both attention and cognitive outcomes. These differences may provide explanation for the lack of significant associations identified for the INTERGROWTH-21<sup>st</sup> cohort in Chapter 5 when all sites were pooled. Fewer associations were identified in low-risk samples compared to descriptive samples, within geographic locations, suggesting that in low-risk mothers, there may be some partial protection against negative attention and cognitive outcomes associated with impaired fetal growth.

## 6.6 References

1. IBM Corp. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp; 2012.

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## **7 Sex differences in the associations between birth anthropometric indices and attention and cognitive outcomes in childhood**

### **Chapter outline**

#### **7.1 Introduction**

##### 7.1.1 Hypotheses

#### **7.2 Methods**

##### 7.2.1 Sample characteristics and measures

##### 7.2.2 Statistical analysis

#### **7.3 Results**

##### 7.3.1 Participants

##### 7.3.2 Descriptive statistical and sex differences in maternal and child characteristics

##### 7.3.3 Associations between fetal growth indices and attention outcomes

##### 7.3.4 Associations between fetal growth indices and cognitive outcomes

##### 7.3.5 Sensitivity, specificity and receiver-operating characteristic (ROC) analysis

#### **7.4 Summary of results**

##### 7.4.1 How this chapter builds on previous chapters

#### **7.5 Conclusions**

#### **7.6 References**

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## **7.1 Introduction**

This chapter addresses the fifth and final aim of this thesis, to examine whether the associations between birth anthropometric indices and attention and cognitive development differs between sexes. Although males and females have been shown to differ in (a) fetal growth<sup>1</sup>, (b) adaptation to adverse intrauterine conditions<sup>2</sup> and (c) childhood neurodevelopment<sup>3</sup>, there has been little research into sex differences in the association between impaired fetal growth and neurodevelopmental outcomes.

To recap results from previous chapters, the results of Chapter 5 showed that stunting was most strongly associated with poorer attention outcomes, compared to other birth anthropometric indices examined. Associations were less consistent across cohorts for cognitive outcomes, however, with stronger associations for stunting in Pelotas and ALSPAC, and for wasting in INTERGROWTH-21st. The results of Chapter 6 showed that there are some differences in associations between the higher-income and lower-income countries for both attention and cognitive outcomes. Associations between stunting and attention outcomes were predominantly identified in higher-income countries, and associations between stunting and wasting and cognitive outcomes were only identified in LMICs.

This chapter will examine whether there are also differences in associations between sexes. The chapter begins with an analysis of sex interaction effects in the associations between birth anthropometric indices and attention and cognitive outcomes, to: 1) establish whether sex has a moderating effect; and 2) justify further analysis. The remainder of the analysis will then examine associations in males and females separately.

### **7.1.1 Hypotheses**

Based on previous research, it is hypothesised that females will show stronger associations between birth anthropometric indices and attention and cognitive outcomes than males.

## 7.2 Methods

### 7.2.1 Sample characteristics and measures

The samples used in this analysis are the 2004 Pelotas Birth Cohort, the ALSPAC cohort, and the INTERGROWTH-21<sup>st</sup> cohort (see section 5.1.1). All children with at least one birth anthropometric measurement and attention or cognitive outcomes were included in the analysis. Information is presented on each of the cohorts in Chapter 3 (sections 3.1-3.3). As in Chapter 5, the birth anthropometric indices were divided into measures of birth weight (BW), stunting, wasting and asymmetry. Attention assessments included the attention subscales of the CBCL<sup>4</sup> at 24 months in the INTERGROWTH-21<sup>st</sup> cohort, and at 48 months in the Pelotas cohort, and the SDQ<sup>5</sup> at 81 months in the ALSPAC cohort. Follow-up assessments of cognition include the INTER-NDA<sup>6</sup> at 24 months in the INTERGROWTH-21<sup>st</sup> cohort, and the WPPSI-R<sup>7</sup> at 48 months in the Pelotas cohort and at 49 months in the ALSPAC cohort. More information on the attention and cognitive assessment procedures are presented in Chapter 3 (sections 3.1.2, 3.2.2, and 3.3.2).

### 7.2.2 Statistical analysis

1. **Sex interactions:** In order to first examine whether there was effect modification by sex, ordinal logistic regression (OLR) analyses were conducted, including a sex\*birth anthropometric measure interaction term. Multiple significant sex interactions in associations between birth anthropometric indices and attention and cognitive outcomes, indicated effect modification by sex. This provided justification for separation by sex in further analyses.
2. **Prevalence comparisons:** The prevalence and descriptive statistics of maternal and child characteristics were calculated for males and females, and between-sex differences assessed using univariate ANOVAs and Pearson  $\chi^2$  tests. The prevalence of birth anthropometric indices and poor attention and cognitive outcomes were

calculated for males and females, with chi-squared analyses used to identify differences between sex.

3. **Hierarchical OLR modelling:** The primary analysis to examine the associations between birth anthropometric indices and attention and cognitive outcomes was hierarchical modelling using OLR (as in Chapter 5), conducted separately for males and females. This allowed assessment of the unadjusted associations between birth anthropometric indices and attention/cognitive outcomes (univariable OLR), and then adjustment for potential maternal, demographic, gestational, perinatal and child nutrition/mother-child morbidity confounders (multivariable OLR). Modelling was adjusted for potential covariables that may affect either the exposure (birth anthropometric measure) or outcome (childhood attention/cognitive outcomes). For inclusion in the model, confounding variables had to be associated with birth anthropometric measures and attention/cognitive outcomes ( $p < 0.20$ ), or have a strong theoretical basis for inclusion<sup>8</sup>.
4. **Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and receiver operating characteristics (ROC) analyses:** Sensitivity, specificity and receiver-operating characteristic (ROC) analyses were conducted separately for each sex, to examine the ability of birth anthropometric indices to predict attention or cognitive outcomes. All analyses were performed using IBM SPSS Statistics for Windows 21.0<sup>9</sup>. Further statistical considerations for statistical analyses are presented in Chapter 3 (section 3.6).

## 7.3 Results

### 7.3.1 Participants

The initial Pelotas sample consisted of 4231 neonates. Data on BW was available for 4228 neonates ( $n_{male} = 2194$  (51.9%);  $n_{female} = 2034$  (48.1%)), BL for 4167 neonates ( $n_{male} = 2159$

(51.8%);  $n_{female}$  = 2008 (48.2%)), HC for 4170 neonates ( $n_{male}$  = 2162 (51.8%);  $n_{female}$  = 2008 (48.2%)) and GA at delivery for 4217 neonates ( $n_{male}$  = 2188 (51.9%);  $n_{female}$  = 2029 (48.1%)). At the 48 month follow-up ( $M$  = 49.53,  $SD$  = 1.72 months), 3749 children were assessed on the attention subscale of the CBCL<sup>4</sup> and the WPPSI-R<sup>7</sup> ( $n_{male}$  = 1943 (51.8%);  $n_{female}$  = 1806 (48.2%); 11.4% attrition). There were no differences between males and females in attrition rates,  $\chi^2 = 0.08$ ,  $p = .809$ .

The initial ALSPAC sample consisted of 14,062 neonates. Data on BW was available for 13,445 neonates ( $n_{male}$  = 6933 (51.6%);  $n_{female}$  = 6512 (48.4%)), BL for 10,252 neonates ( $n_{male}$  = 5268 (51.4%);  $n_{female}$  = 4984 (48.6%)), HC for 10,397 neonates ( $n_{male}$  = 5343 (51.4%);  $n_{female}$  = 5054 (48.6%)) and GA at delivery for 13,616 neonates ( $n_{male}$  = 7023 (51.6%);  $n_{female}$  = 6593 (48.4%)). The attention subscale of the SDQ<sup>5</sup> was assessed in the child-based questionnaire conducted at 81 months ( $M$  = 81.44,  $SD$  = 0.37 months), with valid data on 7828 children ( $n_{male}$  = 3003 (51.9%);  $n_{female}$  = 2785 (48.1%); 44.4% loss). The WPPSI-R<sup>7</sup> was conducted on a smaller focus group of 992 children ( $n_{male}$  = 548 (55.2%);  $n_{female}$  = 444 (44.8%); 7.2% of original sample) at 49 months ( $M$  = 48.85,  $SD$  = 0.37 months). There were no differences between males and female in attrition rate,  $\chi^2 = 0.37$ ,  $p = .544$ .

The total INTERGROWTH-21<sup>st</sup> sample across the UK, Italy, Brazil, India and Kenya sites consisted of 2803 neonates ( $n_{male}$  = 1367 (48.8%);  $n_{female}$  = 1445 (51.2%)). Of these, 1649 infants were eligible for the INTER-NDA<sup>6</sup> at the time of data freezing. The INTER-NDA and attention subscale of the CBCL were conducted at the 24 month follow-up ( $M$  = 24.85,  $SD$  = 2.02 months), with valid CBCL<sup>4</sup> (attention) data on 1076 children (( $n_{male}$  = 553 (49.5%);  $n_{female}$  = 543 (50.5%); 38.4% of original sample) and INTER-NDA<sup>6</sup> (cognitive) data on 1066 children (( $n_{male}$  = 526 (49.3%);  $n_{female}$  = 540 (50.7%); 65.3% of eligible sample). There were no differences between males and female in attrition rates,  $\chi^2 = 0.21$ ,  $p = .644$ .

### **7.3.2 Descriptive statistics and sex differences in maternal and child characteristics**

OLR analyses including birth indices\*sex as an interaction term showed that sex moderated the association between attention (Table 7.1) and cognitive (Table 7.2) outcomes in at least one of the cohorts for all birth anthropometric indices ( $p < .05$ ), with the exception of PI-for-age ( $p > .127$ ). This justified separation by sex in further analyses.



**Table 7.1. Sex interactions of associations between birth anthropometric indices and poorer attention outcomes**

| Variable (N)                             | Pelotas |          | ALSPAC |          | INTERGROWTH-21st |       |
|------------------------------------------|---------|----------|--------|----------|------------------|-------|
|                                          | OR      | <i>p</i> | OR     | <i>p</i> |                  |       |
| <b>Birth weight indices</b>              |         |          |        |          |                  |       |
| BW <2500g                                | 1.20    | .004*    | 1.20   | .005*    | 0.91             | .700  |
| SGA                                      | 1.18    | .002*    | 1.15   | .003*    | 1.05             | .546  |
| BW <10 <sup>th</sup> MGRS                | 1.20    | <.001**  | 1.19   | <.001*   | 0.99             | .343  |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.26    | <.001**  | 1.22   | .001*    | 0.85             | .137  |
| <b>Stunting indices</b>                  |         |          |        |          |                  |       |
| BL < 10 <sup>th</sup> MGRS               | 1.14    | .001*    | 1.21   | .003*    | 1.07             | .514  |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.17    | .001*    | 1.26   | .002*    | 1.29             | .036* |
| HC <10 <sup>th</sup> MGRS                | 1.26    | <.001**  | 1.29   | <.001**  | 1.09             | .400  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.23    | <.001**  | 1.21   | .036*    | 1.01             | .954  |
| <b>Wasting indices</b>                   |         |          |        |          |                  |       |
| PI <10 <sup>th</sup> percentile          | 1.20    | <.001**  | 0.99   | .787     | 1.03             | .805  |
| PI-for-age <10 <sup>th</sup> percentile  | 1.05    | .395     | 0.94   | .210     | 1.02             | .877  |
| BMI <10 <sup>th</sup> percentile         | 1.22    | .002*    | 1.05   | .340     | 1.08             | .545  |
| BMI-for-age <10 <sup>th</sup> percentile | 1.16    | .020*    | 1.03   | .587     | 1.05             | .698  |
| <b>Asymmetry indices</b>                 |         |          |        |          |                  |       |
| HC/BL >90 <sup>th</sup> percentile       | 1.12    | .082     | 1.01   | .885     | 0.92             | .571  |
| HC/PI >90 <sup>th</sup> percentile       | 0.99    | .842     | 0.91   | .071     | 0.91             | .598  |
| HC/BMI >90 <sup>th</sup> percentile      | 1.10    | .129     | 1.03   | .547     | 0.91             | .643  |

OR>1=poorer outcome; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21st = INTERGROWTH-21st growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* =  $p<.05$ ; \*\*= $p<.001$

**Table 7.2. Sex interactions of associations between birth anthropometric indices and poorer cognitive outcomes**

| Variable (N)                             | Pelotas |         | ALSPAC |      | INTERGROWTH-21st |         |
|------------------------------------------|---------|---------|--------|------|------------------|---------|
|                                          | OR      | p       | OR     | p    | OR               | p       |
| <b>Birth weight indices</b>              |         |         |        |      |                  |         |
| BW <2500g                                | 1.39    | <.001** | 1.04   | .839 | 0.82             | .135    |
| SGA                                      | 1.25    | <.001** | 1.05   | .741 | 0.93             | .352    |
| BW <10 <sup>th</sup> MGRS                | 1.31    | <.001** | 1.16   | .337 | 0.65             | <.001** |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.32    | <.001** | 1.22   | .290 | 1.03             | .764    |
| <b>Stunting indices</b>                  |         |         |        |      |                  |         |
| BL < 10 <sup>th</sup> MGRS               | 1.21    | <.001** | 1.23   | .267 | 0.75             | .004*   |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.23    | <.001** | 1.43   | .114 | 1.02             | .886    |
| HC <10 <sup>th</sup> MGRS                | 1.32    | <.001** | 1.17   | .405 | 0.96             | .648    |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.52    | <.001** | 1.44   | .128 | 1.08             | .558    |
| <b>Wasting indices</b>                   |         |         |        |      |                  |         |
| PI <10 <sup>th</sup> percentile          | 1.23    | <.001** | 1.04   | .727 | 1.19             | .163    |
| PI-for-age <10 <sup>th</sup> percentile  | 1.10    | .127    | 1.00   | .967 | 1.20             | .142    |
| BMI <10 <sup>th</sup> percentile         | 1.45    | <.001** | 0.96   | .753 | 1.29             | .035*   |
| BMI-for-age <10 <sup>th</sup> percentile | 1.15    | .025*   | 0.93   | .556 | 1.19             | .133    |
| <b>Asymmetry indices</b>                 |         |         |        |      |                  |         |
| HC/BL >90 <sup>th</sup> percentile       | 1.07    | .285    | 0.97   | .862 | 0.57             | <.001** |
| HC/PI >90 <sup>th</sup> percentile       | 1.01    | .870    | 1.00   | .971 | 0.64             | <.001** |
| HC/BMI >90 <sup>th</sup> percentile      | 1.24    | .001*   | 1.00   | .999 | 0.64             | <.001** |

OR>1=poorer outcome; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21st = INTERGROWTH-21st growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

Comparison between sexes by maternal and child characteristics showed some differences between males and females in all three cohorts (Table S7.1). Differences in maternal characteristics between males and females were revealed in the ALSPAC cohort, with mothers giving birth to males being slightly older at delivery (28.07 compared to 27.85 years), and being more likely to smoke during pregnancy (26.1% compared to 24.3%). There were no differences in maternal characteristics between sexes in the Pelotas 2004 or INTERGROWTH-21<sup>st</sup> cohorts.

Sex differences were identified in child characteristics in all three cohorts. Males were found to have a significantly higher mean BW, BL, and HC, than females, in all three cohorts. Males had a significantly lower PI in both the Pelotas and ALSPAC cohorts, but had a higher BMI in the INTERGROWTH 21<sup>st</sup> cohort. In both ALSPAC and INTERGROWTH-21<sup>st</sup> more male neonates had an APGAR score<7 (1.7% compared to 1.1%, and 0.7% compared to 0.0%, respectively). In ALSPAC, more males were born preterm (5.6% compared to 4.4%), however in INTERGROWTH-21<sup>st</sup>, more females were born preterm (6.3% compared to 1.8%).

There were some differences identified in the prevalence of birth anthropometric indices between sexes (Table 7.3). In Pelotas, males had a lower prevalence of LBW (7.9% compared to 10.3%), a lower prevalence of HC<10<sup>th</sup> percentile by MGRS standards (14.0% compared to 18.5%) and a higher prevalence of asymmetry in HC/BL (11.1% compared to 8.6%), HC/PI (12.7% compared to 7.1%) and HC/BMI (11.1% compared to 8.8%). In ALSPAC, males had a higher prevalence of BW<10<sup>th</sup> percentile according to MGRS standards (10.5% compared to 8.8%), a lower prevalence of HC<10<sup>th</sup> percentile according to INTERGROWTH-21<sup>st</sup> standards (2.0% compared to 2.7%), a higher prevalence of PI<10<sup>th</sup> percentile (10.7% compared to 9.2%) and a higher prevalence of asymmetry indices in HC/BL (10.8% compared to 9.1%), HC/PI (12.0% compared to 7.8%) and HC/BMI (11.4% compared to 8.5%). In INTERGROWTH-21<sup>st</sup>, males had a lower prevalence of LBW (4.5% compared to 8.4%) and small-for-gestational-age (SGA) according to the United States National Reference for Fetal Growth<sup>10</sup> (17.6% compared to 24.7%).

**Table 7.3. Prevalence of impaired fetal and birth anthropometric indices in the INTERGROWTH-21st, ALSPAC and Pelotas cohorts**

| Variable                                 | Pelotas n (%) (N=3508) |            |          | ALSPAC n (%) (N=6768) |            |          | INTERGROWTH-21 <sup>st</sup> n (%) (N=1126) |            |          |
|------------------------------------------|------------------------|------------|----------|-----------------------|------------|----------|---------------------------------------------|------------|----------|
|                                          | Males                  | Females    | $\chi^2$ | Males                 | Females    | $\chi^2$ | Males                                       | Females    | $\chi^2$ |
| <b>Birth weight indices</b>              |                        |            |          |                       |            |          |                                             |            |          |
| BW <2500g                                | 154 (7.9)              | 186 (10.3) | 6.42*    | 295 (4.3)             | 294 (4.5)  | 0.54     | 25 (4.5)                                    | 48 (8.4)   | 7.23*    |
| SGA                                      | 298 (15.3)             | 255 (14.1) | 1.10     | 616 (8.9)             | 538 (8.3)  | 1.66     | 99 (17.6)                                   | 140 (24.7) | 7.77*    |
| BW <10 <sup>th</sup> MGRS                | 351 (18.1)             | 343 (19.0) | 0.55     | 731 (10.5)            | 571 (8.8)  | 12.10*   | 89 (16.0)                                   | 113 (19.9) | 2.88     |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 188 (9.7)              | 172 (9.5)  | 0.03     | 412 (5.9)             | 361 (5.5)  | 0.99     | 59 (10.6)                                   | 76 (13.4)  | 2.04     |
| <b>Stunting indices</b>                  |                        |            |          |                       |            |          |                                             |            |          |
| BL < 10 <sup>th</sup> MGRS               | 549 (28.4)             | 508 (28.2) | 0.01     | 352 (6.7)             | 288 (5.8)  | 3.57     | 71 (12.8)                                   | 85 (15.1)  | 1.24     |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 351 (18.2)             | 349 (19.4) | 0.96     | 202 (3.8)             | 211 (4.2)  | 1.06     | 48 (8.7)                                    | 65 (11.6)  | 2.55     |
| HC <10 <sup>th</sup> MGRS                | 272 (14.0)             | 334 (18.5) | 13.99**  | 287 (5.4)             | 274 (5.4)  | 0.01     | 72 (13.0)                                   | 89 (15.8)  | 1.76     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 131 (6.8)              | 145 (8.1)  | 0.03     | 107 (2.0)             | 135 (2.7)  | 5.11*    | 36 (6.5)                                    | 44 (7.8)   | 0.70     |
| <b>Wasting indices</b>                   |                        |            |          |                       |            |          |                                             |            |          |
| PI <10 <sup>th</sup> percentile          | 194 (10.0)             | 180 (10.0) | 0.00     | 558 (10.7)            | 455 (9.2)  | 6.15*    | 55 (9.9)                                    | 56 (9.9)   | 0.00     |
| PI-for-age <10 <sup>th</sup> percentile  | 188 (9.7)              | 175 (9.7)  | 0.00     | 516 (9.9)             | 493 (10.0) | 0.03     | 55 (9.9)                                    | 54 (9.6)   | 0.04     |
| BMI <10 <sup>th</sup> percentile         | 193 (10.0)             | 179 (10.0) | 0.00     | 520 (10.0)            | 494 (10.0) | 0.01     | 55 (9.9)                                    | 56 (9.9)   | 0.00     |
| BMI-for-age <10 <sup>th</sup> percentile | 189 (9.8)              | 175 (9.7)  | 0.00     | 518 (9.9)             | 490 (9.9)  | 0.00     | 57 (10.2)                                   | 56 (10.0)  | 0.04     |
| <b>Asymmetry indices</b>                 |                        |            |          |                       |            |          |                                             |            |          |
| HC/BL >90 <sup>th</sup> percentile       | 215 (11.1)             | 155 (8.6)  | 6.47*    | 570 (10.8)            | 454 (9.1)  | 8.28*    | 59 (10.6)                                   | 52 (9.2)   | 0.61     |
| HC/PI >90 <sup>th</sup> percentile       | 245 (12.7)             | 128 (7.1)  | 31.83**  | 627 (12.0)            | 386 (7.8)  | 49.53**  | 62 (11.2)                                   | 49 (8.7)   | 1.90     |
| HC/BMI >90 <sup>th</sup> percentile      | 214 (11.1)             | 159 (8.8)  | 5.09*    | 594 (11.4)            | 418 (8.5)  | 23.88**  | 52 (9.4)                                    | 59 (10.5)  | 0.39     |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21st = INTERGROWTH-21st growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

The prevalence of poor attention and cognitive outcomes as a dichotomous variable also differed between sexes across the three cohorts (Figure 7.1), with a higher prevalence of poor attention and cognitive outcomes in males, compared to females, in all three cohorts. In Pelotas and ALSPAC, males had a significantly higher prevalence of poor attention outcomes than females (8.2% compared to 6.3% and 14.3% compared to 7.4%, respectively). The same pattern was identified in INTERGROWTH-21<sup>st</sup> (6.8% compared to 4.4%), however the chi-squared analysis did not reach statistical significance ( $\chi^2 = 2.78$ ,  $p = .062$ ; Table 7.4). Males showed a significantly higher prevalence of poor cognitive outcomes in Pelotas (20.1% compared to 12.8%) and INTERGROWTH-21<sup>st</sup> (25.1% compared to 18.1%). The same pattern was identified in ALSPAC (17.5% compared to 13.1%), however the chi-squared analysis did not reach the threshold of statistical significance ( $\chi^2 = 3.71$ ,  $p = .054$ ).

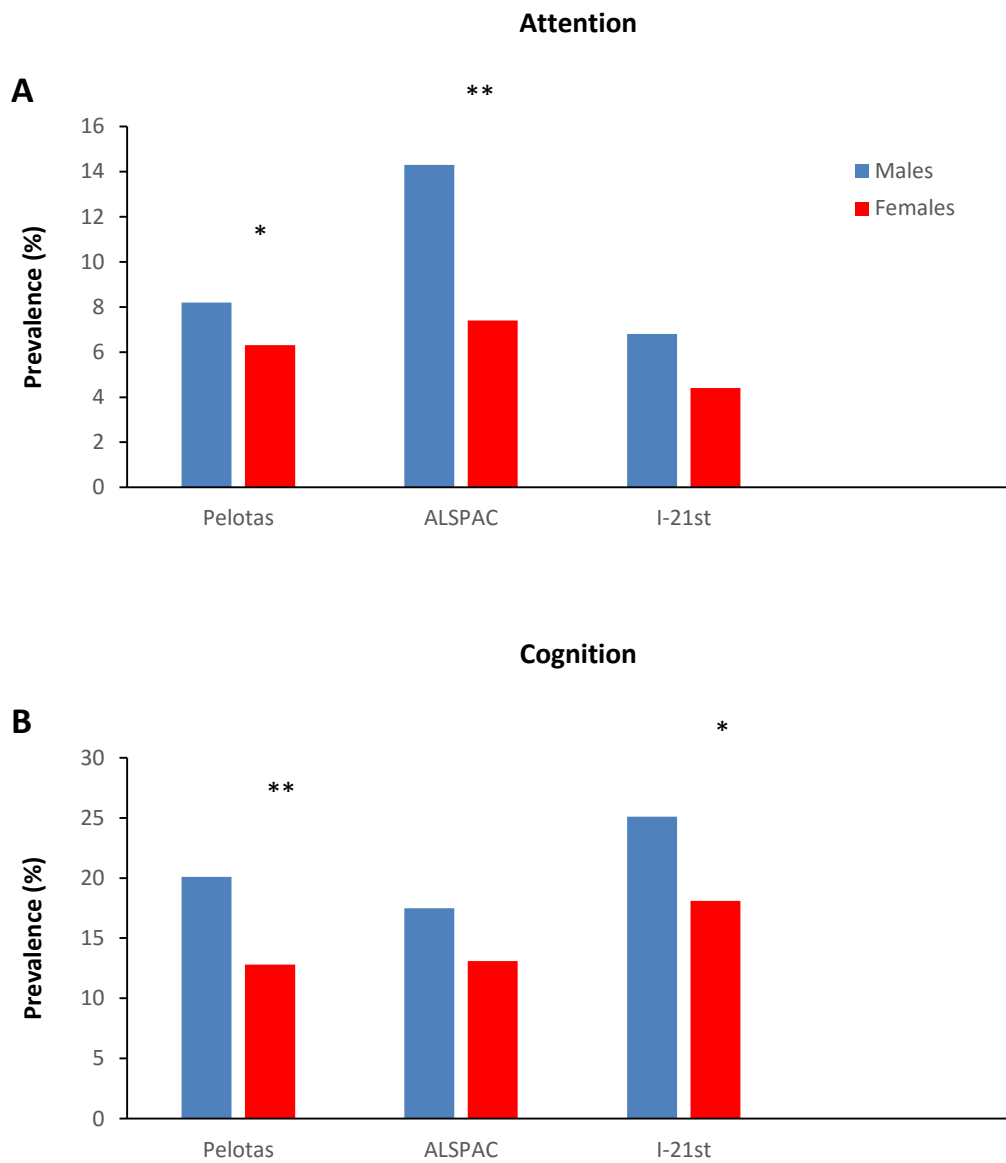


**Figure 7.1. Prevalence (%) of attention impairment (A) and cognitive impairment (B) in males and females in Pelotas, ALSPAC and INTERGROWTH-21<sup>st</sup>. Impairments = SDQ score  $\geq 7$ ; CBCL  $t$  score  $\geq 67$ ; WPPSI score  $>1SD$  below mean; INTER-NDA score  $>1SD$  below mean; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup>; \* =  $p < .05$ ; \*\* =  $p < .001$ ; \* =  $p < .05$ ; \*\* =  $p < .001$**

**Table 7.4. Prevalence of impaired fetal and birth anthropometric indices in the INTERGROWTH-21st, ALSPAC and Pelotas cohorts**

|                                             | Attention  | Cognitive  |
|---------------------------------------------|------------|------------|
| <b>Pelotas (N=3508)</b>                     |            |            |
| Males n(%)                                  | 159 (8.2)  | 391 (20.1) |
| Females n(%)                                | 114 (6.3)  | 232 (12.8) |
| $\chi^2$                                    | 4.85*      | 35.78**    |
| <b>ALSPAC (N=6786)</b>                      |            |            |
| Males n(%)                                  | 576 (14.3) | 96 (17.5)  |
| Females n(%)                                | 282 (7.4)  | 58 (13.1)  |
| $\chi^2$                                    | 96.04**    | 3.71       |
| <b>INTERGROWTH-21<sup>st</sup> (N=1126)</b> |            |            |
| Males n(%)                                  | 36 (6.8)   | 132 (25.1) |
| Females n(%)                                | 24 (4.4)   | 98 (18.1)  |
| $\chi^2$                                    | 2.78       | 7.60*      |

Impairments = SDQ score  $\geq 7$ ; CBCL *t* score  $\geq 67$ ; WPPSI score  $>1SD$

below mean; INTER-NDA score  $>1SD$  below mean \* =  $p < .05$ ;

\*\*= $p < .001$ ; \* =  $p < .05$ ; \*\*= $p < .001$

### 7.3.3 Associations between fetal growth indices and attention outcomes

Table 7.5-Table 7.10 present the results of the univariable and multivariable OLR analyses, adjusted for maternal/demographic variables, gestational variables, perinatal variables and childhood/nutrition variables. Associations between birth anthropometric indices and attention outcomes were conducted separately for males and females.

In Pelotas, significant unadjusted associations in males were only identified in one index of BW (BW $<10^{\text{th}}$  I-21<sup>st</sup>) and in three indices of stunting (BL $<10^{\text{th}}$  MGRS, BL $<10^{\text{th}}$  I-21<sup>st</sup> and HC $<10^{\text{th}}$  MGRS; Table 7.5). After full adjustment, associations remained only for two stunting indices (BL $<10^{\text{th}}$  MGRS and BL $<10^{\text{th}}$  I-21<sup>st</sup>). In females, significant unadjusted associations were identified for all four indices of BW (BW $<2500g$ , SGA, BW $<10^{\text{th}}$  MGRS and BW $<10^{\text{th}}$  I-21<sup>st</sup>), stunting (BL $<10^{\text{th}}$  MGRS, BL $<10^{\text{th}}$  I-21<sup>st</sup>, HC $<10^{\text{th}}$  MGRS and HC $<10^{\text{th}}$  I-21<sup>st</sup>) and wasting (PI $<10^{\text{th}}$  percentile, PI-for-

age <10<sup>th</sup> percentile, BMI<10<sup>th</sup> percentile and BMI-for-age <10<sup>th</sup> percentile; Table 7.6). After full adjustment, significant associations remained for three BW indices (BW<2500g<2500g, SGA and BW<10<sup>th</sup> MGRS), three stunting indices (BL<10<sup>th</sup> MGRS, HC<10<sup>th</sup> MGRS and HC<10<sup>th</sup> I-21<sup>st</sup>), and all four wasting indices (PI<10<sup>th</sup> percentile, PI-for-age <10<sup>th</sup> percentile, BMI<10<sup>th</sup> percentile, BMI-for-age<10<sup>th</sup> percentile). In sum, there were significant fully adjusted associations in two indices in males compared to ten indices in females for poorer attention outcomes. The strongest associations were BL<10<sup>th</sup> I-21<sup>st</sup> for males (OR=1.27,  $p=.024$ ), and HC<10<sup>th</sup> percentile MGRS for females (OR=1.58,  $p<.001$ ). This means that the odds of males with a BL<10th percentile having a poorer attention score was 1.27 times that of males with normal BL, and that the odds of females with a HC<10th percentile having a poorer attention score was 1.58 times that of females with normal HC. These were both small, but statistically significant effects.



**Table 7.5. Unadjusted and adjusted associations between birth anthropometric indices and higher attention score in childhood in Pelotas in males**

| Variables                                | Unadjusted |           |          | Fully adjusted |           |          |
|------------------------------------------|------------|-----------|----------|----------------|-----------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI     | <i>p</i> |
| <b>Birth weight indices</b>              |            |           |          |                |           |          |
| BW <2500g                                | 1.18       | 0.88-1.58 | .265     | 1.03           | 0.76-1.39 | .870     |
| SGA                                      | 1.15       | 0.93-1.43 | .208     | 1.07           | 0.86-1.34 | .552     |
| BW <10 <sup>th</sup> MGRS                | 1.12       | 0.91-1.37 | .275     | 1.00           | 0.81-1.23 | .999     |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.44       | 1.11-1.88 | .007*    | 1.31           | 1.00-1.71 | .054     |
| <b>Stunting indices</b>                  |            |           |          |                |           |          |
| BL < 10 <sup>th</sup> MGRS               | 1.28       | 1.08-1.52 | .005*    | 1.22           | 1.03-1.46 | .026*    |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.33       | 1.09-1.63 | .005*    | 1.27           | 1.03-1.56 | .024*    |
| HC <10 <sup>th</sup> MGRS                | 1.39       | 1.11-1.74 | .004*    | 1.24           | 0.99-1.57 | .066     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.27       | 0.94-1.73 | .124     | 1.12           | 0.82-1.54 | .482     |
| <b>Wasting indices</b>                   |            |           |          |                |           |          |
| PI <10 <sup>th</sup> percentile          | 1.11       | 0.85-1.43 | .447     | 0.99           | 0.76-1.28 | .912     |
| PI-for-age <10 <sup>th</sup> percentile  | 0.88       | 0.68-1.14 | .349     | 0.82           | 0.63-1.06 | .134     |
| BMI <10 <sup>th</sup> percentile         | 1.17       | 0.91-1.52 | .228     | 1.01           | 0.77-1.32 | .955     |
| BMI-for-age <10 <sup>th</sup> percentile | 1.06       | 0.81-1.37 | .686     | 0.96           | 0.74-1.26 | .784     |
| <b>Asymmetry indices</b>                 |            |           |          |                |           |          |
| HC/BL >90 <sup>th</sup> percentile       | 1.27       | 0.99-1.63 | .058     | 1.25           | 0.97-1.62 | .082     |
| HC/PI >90 <sup>th</sup> percentile       | 0.95       | 0.75-1.20 | .665     | 0.94           | 0.74-1.19 | .592     |
| HC/BMI >90 <sup>th</sup> percentile      | 1.13       | 0.88-1.45 | .338     | 1.01           | 0.78-1.30 | .934     |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

**Table 7.6. Unadjusted and adjusted associations between birth anthropometric indices and higher attention score in childhood in Pelotas in females**

| Variables                                | Unadjusted |           |         | Fully adjusted |           |         |
|------------------------------------------|------------|-----------|---------|----------------|-----------|---------|
|                                          | OR         | 95%CI     | p       | OR             | 95%CI     | p       |
| <b>Birth weight indices</b>              |            |           |         |                |           |         |
| BW <2500g                                | 1.65       | 1.26-2.17 | <.001** | 1.47           | 1.10-1.96 | .009*   |
| SGA                                      | 1.56       | 1.23-1.97 | <.001** | 1.40           | 1.10-1.79 | .006*   |
| BW <10 <sup>th</sup> MGRS                | 1.71       | 1.39-2.10 | <.001** | 1.56           | 1.25-1.94 | <.001** |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.61       | 1.21-2.14 | .001*   | 1.34           | 1.00-1.80 | .053    |
| <b>Stunting indices</b>                  |            |           |         |                |           |         |
| BL <10 <sup>th</sup> MGRS                | 1.29       | 1.16-1.67 | <.001** | 1.21           | 1.01-1.47 | .044*   |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.44       | 1.17-1.77 | .001*   | 1.24           | 1.00-1.54 | .049*   |
| HC <10 <sup>th</sup> MGRS                | 1.76       | 1.43-2.18 | <.001** | 1.58           | 1.27-1.96 | <.001** |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.67       | 1.24-2.26 | .001*   | 1.47           | 1.08-2.01 | .013*   |
| <b>Wasting indices</b>                   |            |           |         |                |           |         |
| PI <10 <sup>th</sup> percentile          | 1.42       | 1.08-1.88 | .012*   | 1.35           | 1.02-1.79 | .036*   |
| PI-for-age <10 <sup>th</sup> percentile  | 1.35       | 1.02-1.79 | .033*   | 1.34           | 1.00-1.78 | .048*   |
| BMI <10 <sup>th</sup> percentile         | 1.68       | 1.27-2.22 | <.001** | 1.52           | 1.14-2.04 | .005*   |
| BMI-for-age <10 <sup>th</sup> percentile | 1.57       | 1.18-2.07 | .002*   | 1.54           | 1.16-2.06 | .003*   |
| <b>Asymmetry indices</b>                 |            |           |         |                |           |         |
| HC/BL >90 <sup>th</sup> percentile       | 1.23       | 0.92-1.64 | .171    | 1.14           | 0.85-1.54 | .379    |
| HC/PI >90 <sup>th</sup> percentile       | 1.03       | 0.75-1.41 | .871    | 1.02           | 0.74-1.41 | .900    |
| HC/BMI >90 <sup>th</sup> percentile      | 1.29       | 0.97-1.71 | .084    | 1.31           | 0.97-1.77 | .073    |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

In ALSPAC, significant unadjusted associations in males were only identified in two stunting indices (BL<10<sup>th</sup> I-21<sup>st</sup> and HC<10<sup>th</sup> MGRS) and one wasting index (BMI-for-age<10<sup>th</sup> percentile; Table 7.7), with poorer attention outcomes. After full adjustment, no significant associations remained between any birth anthropometric indices and attention outcomes. In females, significant unadjusted associations were identified for all four indices of BW (BW<2500g, SGA, BW<10<sup>th</sup> MGRS and BW<10<sup>th</sup> I-21<sup>st</sup>), and all four indices of stunting (BL<10<sup>th</sup> MGRS, BL<10<sup>th</sup> I-21<sup>st</sup>, HC<10<sup>th</sup> MGRS and HC<10<sup>th</sup> I-21<sup>st</sup>), and one index of wasting (BMI<10<sup>th</sup> percentile; Table 7.8). After full adjustment, association remained for all four indices of BW (BW<2500g, SGA, BW<10<sup>th</sup> MGRS and BW<10<sup>th</sup> I-21<sup>st</sup>), and one index of stunting (HC<10<sup>th</sup> MGRS). In sum, there were no significant fully adjusted associations in males compared to five in females for poorer attention outcomes. The strongest association for females was HC<10<sup>th</sup> MGRS (OR=1.60,  $p=.010$ ).

**Table 7.7. Unadjusted and adjusted associations between birth anthropometric indices and higher attention score in childhood in ALSPAC in males**

| Variables                                | Unadjusted |           |          | Fully adjusted |           |          |
|------------------------------------------|------------|-----------|----------|----------------|-----------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI     | <i>p</i> |
| <b>Birth weight indices</b>              |            |           |          |                |           |          |
| BW <2500g                                | 1.33       | 0.99-1.79 | .058     | 1.21           | 0.86-1.72 | .271     |
| SGA                                      | 1.13       | 0.92-1.38 | .243     | 1.01           | 0.80-1.28 | .915     |
| BW <10 <sup>th</sup> MGRS                | 1.20       | 1.00-1.45 | .053     | 1.06           | 0.84-1.32 | .632     |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.24       | 0.97-1.59 | .089     | 1.16           | 0.86-1.55 | .326     |
| <b>Stunting indices</b>                  |            |           |          |                |           |          |
| BL < 10 <sup>th</sup> MGRS               | 1.20       | 0.93-1.55 | .157     | 1.12           | 0.84-1.50 | .450     |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.55       | 1.11-2.16 | .010*    | 1.29           | 0.88-1.89 | .198     |
| HC <10 <sup>th</sup> MGRS                | 1.39       | 1.05-1.85 | .023*    | 1.20           | 0.85-1.68 | .299     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.17       | 0.76-1.79 | .488     | 1.10           | 0.66-1.85 | .718     |
| <b>Wasting indices</b>                   |            |           |          |                |           |          |
| PI <10 <sup>th</sup> percentile          | 1.21       | 0.99-1.48 | .057     | 1.18           | 0.94-1.49 | .151     |
| PI-for-age <10 <sup>th</sup> percentile  | 1.20       | 0.98-1.47 | .077     | 1.20           | 0.95-1.51 | .137     |
| BMI <10 <sup>th</sup> percentile         | 1.14       | 0.92-1.40 | .223     | 1.09           | 0.86-1.39 | .465     |
| BMI-for-age <10 <sup>th</sup> percentile | 1.25       | 1.01-1.54 | .037*    | 1.17           | 0.92-1.49 | .202     |
| <b>Asymmetry indices</b>                 |            |           |          |                |           |          |
| HC/BL >90 <sup>th</sup> percentile       | 1.12       | 0.91-1.36 | .290     | 1.24           | 0.98-1.56 | .070     |
| HC/PI >90 <sup>th</sup> percentile       | 0.94       | 0.78-1.13 | .495     | 0.90           | 0.73-1.11 | .323     |
| HC/BMI >90 <sup>th</sup> percentile      | 1.04       | 0.86-1.26 | .682     | 0.96           | 0.77-1.21 | .744     |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

**Table 7.8. Unadjusted and adjusted associations between birth anthropometric indices and higher attention score in childhood in ALSPAC in females**

| Variables                                | Unadjusted |           |          | Fully adjusted |           |          |
|------------------------------------------|------------|-----------|----------|----------------|-----------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI     | <i>p</i> |
| <b>Birth weight indices</b>              |            |           |          |                |           |          |
| BW <2500g                                | 1.67       | 1.25-2.24 | .001*    | 1.41           | 1.00-1.99 | .048*    |
| SGA                                      | 1.59       | 1.28-1.98 | <.001**  | 1.33           | 1.02-1.72 | .028*    |
| BW <10 <sup>th</sup> MGRS                | 1.63       | 1.31-2.02 | <.001**  | 1.34           | 1.03-1.76 | .031*    |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.76       | .136-2.28 | <.001**  | 1.39           | 1.02-1.90 | .035*    |
| <b>Stunting indices</b>                  |            |           |          |                |           |          |
| BL < 10 <sup>th</sup> MGRS               | 1.70       | 1.28-2.26 | <.001**  | 1.41           | 1.00-1.99 | .049*    |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.73       | 1.25-2.39 | .001*    | 1.26           | 0.85-1.86 | .255     |
| HC <10 <sup>th</sup> MGRS                | 1.92       | 1.44-2.56 | <.001**  | 1.60           | 1.12-2.28 | .010*    |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.82       | 1.23-2.70 | .003*    | 1.46           | 0.89-2.40 | .131     |
| <b>Wasting indices</b>                   |            |           |          |                |           |          |
| PI <10 <sup>th</sup> percentile          | 0.99       | 0.80-1.23 | .927     | 0.89           | 0.69-1.15 | .383     |
| PI-for-age <10 <sup>th</sup> percentile  | 0.91       | 0.74-1.13 | .387     | 0.87           | 0.68-1.11 | .264     |
| BMI <10 <sup>th</sup> percentile         | 1.24       | 1.00-1.54 | .049*    | 1.04           | 0.81-1.35 | .739     |
| BMI-for-age <10 <sup>th</sup> percentile | 1.11       | 0.89-1.38 | .343     | 0.99           | 0.76-1.28 | .924     |
| <b>Asymmetry indices</b>                 |            |           |          |                |           |          |
| HC/BL >90 <sup>th</sup> percentile       | 1.11       | 0.90-1.28 | .335     | 1.15           | 0.90-1.47 | .257     |
| HC/PI >90 <sup>th</sup> percentile       | 0.85       | 0.68-1.08 | .192     | 0.80           | 0.61-1.04 | .098     |
| HC/BMI >90 <sup>th</sup> percentile      | 1.17       | 0.93-1.47 | .183     | 1.09           | 0.83-1.43 | .537     |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

In INTERGROWTH-21<sup>st</sup>, a significant unadjusted association in males was identified between one index of wasting (PI-for-age<10<sup>th</sup> percentile; Table 7.9) and poorer attention outcomes. After full adjustment, no significant associations remained between any birth anthropometric indices and attention outcomes. In females, a significant unadjusted association was identified in one index of stunting (BL<10<sup>th</sup> I-21<sup>st</sup>; Table 7.10). After full adjustment, this association remained significant. Thus, there were no significant fully adjusted associations in males compared to one in females, BL<10<sup>th</sup> MGRS (OR=1.69,  $p=.040$ ) for poorer attention outcomes. This means that the odds of females with a BL<10<sup>th</sup> percentile having a poorer attention score was 1.69 times that of females with normal BL. This is a small, but statistically significant effect. A supplementary analysis was conducted to examine sex differences across INTERGROWTH-21<sup>st</sup> sites (Table S7.2). Overall, when separated by INTERGROWTH-21<sup>st</sup> site, 10 associations were identified in females compared to 2 in males, predominantly in indices of stunting. Stronger associations between stunting and poorer attention outcomes in females were identified across high-, middle- and low-income countries (UK, Brazil and Kenya).

**Table 7.9. Unadjusted and adjusted associations between birth anthropometric indices and higher attention score in childhood for INTERGROWTH-21st in males**

| Variables                                | Unadjusted |           |          | Fully adjusted |           |          |
|------------------------------------------|------------|-----------|----------|----------------|-----------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI     | <i>p</i> |
| <b>Birth weight indices</b>              |            |           |          |                |           |          |
| BW <2500g                                | 1.20       | 0.52-2.74 | .667     | 0.95           | 0.44-2.08 | .906     |
| SGA                                      | 0.91       | 0.62-1.34 | .641     | 0.82           | 0.55-1.24 | .357     |
| BW <10 <sup>th</sup> MGRS                | 1.27       | 0.83-1.92 | .270     | 1.12           | 0.73-1.71 | .602     |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.47       | 0.90-2.42 | .128     | 1.36           | 0.82-2.23 | .227     |
| <b>Stunting indices</b>                  |            |           |          |                |           |          |
| BL < 10 <sup>th</sup> MGRS               | 0.84       | 0.65-1.70 | .840     | 0.94           | 0.59-1.50 | .805     |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.78       | 0.45-1.34 | .364     | 0.79           | 0.46-1.36 | .398     |
| HC <10 <sup>th</sup> MGRS                | 1.33       | 0.85-2.11 | .215     | 1.20           | 0.72-1.80 | .586     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.30       | 0.71-2.38 | .390     | 1.16           | 0.63-2.13 | .642     |
| <b>Wasting indices</b>                   |            |           |          |                |           |          |
| PI <10 <sup>th</sup> percentile          | 1.40       | 0.84-2.31 | .195     | 1.24           | 0.74-2.07 | .407     |
| PI-for-age <10 <sup>th</sup> percentile  | 1.70       | 1.03-2.80 | .040*    | 1.59           | 0.95-2.66 | .077     |
| BMI <10 <sup>th</sup> percentile         | 1.49       | 0.90-2.46 | .119     | 1.29           | 0.76-2.18 | .340     |
| BMI-for-age <10 <sup>th</sup> percentile | 1.34       | 0.82-2.18 | .248     | 1.23           | 0.74-2.04 | .423     |
| <b>Asymmetry indices</b>                 |            |           |          |                |           |          |
| HC/BL >90 <sup>th</sup> percentile       | 0.74       | 0.45-1.22 | .236     | 0.81           | 0.49-1.34 | .415     |
| HC/PI >90 <sup>th</sup> percentile       | 1.32       | 0.81-2.12 | .263     | 1.16           | 0.72-1.89 | .522     |
| HC/BMI >90 <sup>th</sup> percentile      | 1.28       | 0.76-2.16 | .348     | 1.12           | 0.66-1.88 | .678     |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

**Table 7.10. Unadjusted and adjusted associations between birth anthropometric indices and higher attention score in childhood for INTERGROWTH-21st in females**

| Variables                                | Unadjusted |           |          | Fully adjusted |           |          |
|------------------------------------------|------------|-----------|----------|----------------|-----------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI     | <i>p</i> |
| <b>Birth weight indices</b>              |            |           |          |                |           |          |
| BW <2500g                                | 0.84       | 0.49-1.42 | .506     | 0.71           | 0.32-1.56 | .392     |
| SGA                                      | 1.12       | 0.79-1.58 | .537     | 1.06           | 0.74-1.52 | .765     |
| BW <10 <sup>th</sup> MGRS                | 1.19       | 0.81-1.74 | .377     | 0.87           | 0.56-1.36 | .551     |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.72       | 0.47-1.11 | .139     | 0.68           | 0.43-1.07 | .097     |
| <b>Stunting indices</b>                  |            |           |          |                |           |          |
| BL < 10 <sup>th</sup> MGRS               | 1.15       | 0.76-1.73 | .517     | 1.02           | 0.64-1.63 | .938     |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.67       | 1.04-2.68 | .035*    | 1.69           | 1.02-2.78 | .040*    |
| HC <10 <sup>th</sup> MGRS                | 1.20       | 0.79-1.82 | .395     | 0.91           | 0.57-1.46 | .696     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.02       | 0.58-1.81 | .944     | 0.90           | 0.50-1.63 | .729     |
| <b>Wasting indices</b>                   |            |           |          |                |           |          |
| PI <10 <sup>th</sup> percentile          | 1.07       | 0.65-1.78 | .789     | 0.85           | 0.50-1.46 | .552     |
| PI-for-age <10 <sup>th</sup> percentile  | 1.05       | 0.62-1.77 | .865     | 0.88           | 0.51-1.51 | .633     |
| BMI <10 <sup>th</sup> percentile         | 1.17       | 0.71-1.92 | .538     | 0.89           | 0.52-1.53 | .671     |
| BMI-for-age <10 <sup>th</sup> percentile | 1.11       | 0.67-1.82 | .686     | 1.01           | 0.60-1.66 | .997     |
| <b>Asymmetry indices</b>                 |            |           |          |                |           |          |
| HC/BL >90 <sup>th</sup> percentile       | 0.97       | 0.59-1.61 | .916     | 0.98           | 0.57-1.69 | .944     |
| HC/PI >90 <sup>th</sup> percentile       | 0.73       | 0.43-1.25 | .253     | 0.62           | 0.35-1.10 | .101     |
| HC/BMI >90 <sup>th</sup> percentile      | 0.83       | 0.51-1.35 | .454     | 0.66           | 0.39-1.13 | .134     |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age



Table 7.11 shows the direction and statistical significance of associations across all three cohorts. Overall there were many more associations with birth anthropometric indices and poorer attention outcomes for females (19 across all three cohorts) than for males (2 only, both in Pelotas). The strongest associations for females in all three cohorts were identified in indices of stunting, HC and BL in Pelotas and ALSPAC, and BL in INTERGROWTH-21<sup>st</sup> (OR range = 1.24-1.69). Separation by INTERGROWTH-21<sup>st</sup> site identified stronger effects in females evident in high-, middle- and low-income countries.

**Table 7.11. Significant adjusted associations between birth anthropometric indices and higher attention score in Pelotas, ALSPAC and INTERGROWTH-21st in males and females**

| Variable                                 | Males   |        |        | Females |        |        |
|------------------------------------------|---------|--------|--------|---------|--------|--------|
|                                          | Pelotas | ALSPAC | I-21st | Pelotas | ALSPAC | I-21st |
| <b>BW indices</b>                        |         |        |        |         |        |        |
| BW <2500g                                | +       | +      | -      | +       | +      | -      |
| SGA                                      | +       | +      | -      | +       | +      | +      |
| BW <10 <sup>th</sup> MGRS                | +       | +      | +      | +       | +      | -      |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | +       | +      | +      | +       | +      | -      |
| <b>Stunting indices</b>                  |         |        |        |         |        |        |
| BL <10 <sup>th</sup> MGRS                | +       | +      | -      | +       | +      | +      |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | +       | +      | -      | +       | +      | +      |
| HC <10 <sup>th</sup> MGRS                | +       | +      | +      | +       | +      | -      |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | +       | +      | +      | +       | +      | -      |
| <b>Wasting indices</b>                   |         |        |        |         |        |        |
| PI <10 <sup>th</sup> percentile          | -       | +      | +      | +       | -      | -      |
| PI-for-age <10 <sup>th</sup> percentile  | -       | +      | +      | +       | -      | -      |
| BMI <10 <sup>th</sup> percentile         | +       | +      | +      | +       | +      | -      |
| BMI-for-age <10 <sup>th</sup> percentile | -       | +      | +      | +       | -      | +      |
| <b>Asymmetry indices</b>                 |         |        |        |         |        |        |
| HC/BL >90 <sup>th</sup> percentile       | +       | +      | -      | +       | +      | -      |
| HC/PI >90 <sup>th</sup> percentile       | -       | -      | +      | +       | -      | -      |
| HC/BMI >90 <sup>th</sup> percentile      | +       | -      | +      | +       | +      | -      |

+ = OR > 1.00 (positive association); - = OR < 1.00 (negative association); OR > 1 = poorer outcome; \* = p < .05; \*\* = p < .001

### 7.3.4 Associations between fetal growth indices and cognitive outcomes

Table 7.12-Table 7.17 present the results of the univariable and multivariable OLR analyses, adjusted for maternal/demographic variables, gestational variables, perinatal variables and childhood/nutrition variables. Associations between birth anthropometric indices and poorer cognitive outcomes were conducted separately for males and females. In Pelotas, significant unadjusted associations in males were identified in all four indices of BW (BW < 2500g,

SGA, BW<10<sup>th</sup> MGRS and BW<10<sup>th</sup> I-21<sup>st</sup>), all four indices of stunting (BL<10<sup>th</sup> MGRS, BL<10<sup>th</sup> I-21<sup>st</sup>, HC<10<sup>th</sup> MGRS and HC<10<sup>th</sup> I-21<sup>st</sup>), three indices of wasting (PI <10<sup>th</sup> percentile, BMI <10<sup>th</sup> percentile and BMI-for-age <10<sup>th</sup> percentile), and two indices of asymmetry (HC/BL >90<sup>th</sup> percentile and HC/BMI >90<sup>th</sup> percentile; Table 7.12). After full adjustment, associations remained between poorer cognitive outcomes and all four indices of BW (BW<2500g, SGA, BW<10<sup>th</sup> MGRS and BW<10<sup>th</sup> I-21<sup>st</sup>), all four indices of stunting (BL<10<sup>th</sup> MGRS, BL<10<sup>th</sup> I-21<sup>st</sup>, HC<10<sup>th</sup> MGRS and HC<10<sup>th</sup> I-21<sup>st</sup>), one index of wasting (BMI <10<sup>th</sup> percentile), and two indices of asymmetry (HC/BL >90<sup>th</sup> percentile and HC/BMI >90<sup>th</sup> percentile).

In females, significant unadjusted associations were identified between poorer cognitive outcomes and all four indices of BW (BW<2500g, SGA, BW<10<sup>th</sup> MGRS and BW<10<sup>th</sup> I-21<sup>st</sup>), all four indices of stunting (BL<10<sup>th</sup> MGRS, BL<10<sup>th</sup> I-21<sup>st</sup>, HC<10<sup>th</sup> MGRS and HC<10<sup>th</sup> I-21<sup>st</sup>), three indices of wasting (PI<10<sup>th</sup> percentile, BMI<10<sup>th</sup> percentile and BMI-for-age<10<sup>th</sup> percentile), and one index of asymmetry (HC/BMI>90<sup>th</sup> percentile; Table 7.13). After full adjustment, associations remained for three indices of BW (BW<2500g, SGA and BW<10<sup>th</sup> MGRS), all four indices of stunting (BL<10<sup>th</sup> MGRS, BL<10<sup>th</sup> I-21<sup>st</sup>, HC<10<sup>th</sup> MGRS and HC<10<sup>th</sup> I-21<sup>st</sup>), two indices of wasting (PI<10<sup>th</sup> percentile and BMI<10<sup>th</sup> percentile), and one index of asymmetry (HC/BMI>90<sup>th</sup> percentile). In sum, there were significant fully adjusted associations between poorer cognitive outcomes and eleven birth anthropometric indices in males compared to ten birth anthropometric indices in females. The strongest associations were HC<10<sup>th</sup> percentile for both males (OR=1.80,  $p<.001$ ) and females (OR=1.91,  $p<.001$ ).

**Table 7.12. Unadjusted and adjusted associations between birth anthropometric indices and lower cognitive score in childhood in Pelotas in males**

| Variables                                | Unadjusted |           |         | Fully adjusted |           |         |
|------------------------------------------|------------|-----------|---------|----------------|-----------|---------|
|                                          | OR         | 95%CI     | p       | OR             | 95%CI     | p       |
| <b>Birth weight indices</b>              |            |           |         |                |           |         |
| BW <2500g                                | 1.71       | 1.26-2.32 | .001*   | 1.51           | 1.11-2.07 | .010*   |
| SGA                                      | 1.60       | 1.28-2.00 | <.001** | 1.40           | 1.11-1.76 | .004*   |
| BW <10 <sup>th</sup> MGRS                | 1.66       | 1.34-2.05 | <.001** | 1.41           | 1.14-1.76 | .002*   |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.84       | 1.40-2.41 | <.001** | 1.56           | 1.18-2.07 | .002*   |
| <b>Stunting indices</b>                  |            |           |         |                |           |         |
| BL < 10 <sup>th</sup> MGRS               | 1.71       | 1.43-2.05 | <.001** | 1.61           | 1.34-1.94 | <.001** |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.66       | 1.35-2.05 | <.001** | 1.60           | 1.27-1.95 | <.001** |
| HC <10 <sup>th</sup> MGRS                | 2.07       | 1.63-2.62 | <.001** | 1.80           | 1.41-2.30 | <.001** |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.06       | 1.49-2.86 | <.001** | 1.73           | 1.24-2.42 | .001*   |
| <b>Wasting indices</b>                   |            |           |         |                |           |         |
| PI <10 <sup>th</sup> percentile          | 1.59       | 1.22-2.08 | .001*   | 1.29           | 0.98-1.70 | .070    |
| PI-for-age <10 <sup>th</sup> percentile  | 1.19       | 0.91-1.57 | .206    | 0.96           | 0.73-1.28 | .798    |
| BMI <10 <sup>th</sup> percentile         | 1.77       | 1.35-2.32 | <.001** | 1.40           | 1.05-1.85 | .020*   |
| BMI-for-age <10 <sup>th</sup> percentile | 1.33       | 1.01-1.74 | .042*   | 1.11           | 0.84-1.46 | .480    |
| <b>Asymmetry indices</b>                 |            |           |         |                |           |         |
| HC/BL >90 <sup>th</sup> percentile       | 1.42       | 1.10-1.84 | .008*   | 1.51           | 1.16-1.98 | .003*   |
| HC/PI >90 <sup>th</sup> percentile       | 0.95       | 0.75-1.21 | .698    | 0.86           | 0.67-1.10 | .224    |
| HC/BMI >90 <sup>th</sup> percentile      | 1.60       | 1.23-2.07 | <.001** | 1.33           | 1.01-1.74 | .039*   |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

**Table 7.13. Unadjusted and adjusted associations between birth anthropometric indices and lower cognitive score in childhood in Pelotas in females**

| Variables                                | Unadjusted |           |         | Fully adjusted |           |         |
|------------------------------------------|------------|-----------|---------|----------------|-----------|---------|
|                                          | OR         | 95%CI     | p       | OR             | 95%CI     | p       |
| <b>Birth weight indices</b>              |            |           |         |                |           |         |
| BW <2500g                                | 2.12       | 1.60-2.82 | <.001** | 1.90           | 1.43-2.60 | <.001** |
| SGA                                      | 1.51       | 1.19-1.93 | .001*   | 1.34           | 1.04-1.72 | .025*   |
| BW <10 <sup>th</sup> MGRS                | 1.80       | 1.45-2.23 | <.001** | 1.64           | 1.31-2.06 | <.001** |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.61       | 1.21-2.16 | .001*   | 1.30           | 0.96-1.76 | .090    |
| <b>Stunting indices</b>                  |            |           |         |                |           |         |
| BL < 10 <sup>th</sup> MGRS               | 1.43       | 1.18-1.73 | <.001** | 1.27           | 1.04-1.55 | .018*   |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.48       | 1.19-1.83 | <.001** | 1.28           | 1.02-1.60 | .032*   |
| HC <10 <sup>th</sup> MGRS                | 2.15       | 1.72-2.68 | <.001** | 1.91           | 1.51-2.38 | <.001** |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.35       | 1.72-3.22 | <.001** | 1.90           | 1.37-2.63 | <.001** |
| <b>Wasting indices</b>                   |            |           |         |                |           |         |
| PI <10 <sup>th</sup> percentile          | 1.62       | 1.23-2.14 | .001*   | 1.46           | 1.10-1.96 | .010*   |
| PI-for-age <10 <sup>th</sup> percentile  | 1.30       | 0.98-1.72 | .065    | 1.19           | 0.88-1.59 | .258    |
| BMI <10 <sup>th</sup> percentile         | 2.15       | 1.61-2.87 | <.001** | 1.89           | 1.41-2.60 | <.001** |
| BMI-for-age <10 <sup>th</sup> percentile | 1.38       | 1.04-1.83 | .026*   | 1.27           | 0.94-1.70 | .118    |
| <b>Asymmetry indices</b>                 |            |           |         |                |           |         |
| HC/BL >90 <sup>th</sup> percentile       | 1.03       | 0.77-1.39 | .840    | 1.07           | 0.78-1.47 | .663    |
| HC/PI >90 <sup>th</sup> percentile       | 1.11       | 0.81-1.53 | .527    | 1.03           | 0.74-1.44 | .847    |
| HC/BMI >90 <sup>th</sup> percentile      | 1.43       | 1.06-1.92 | .020*   | 1.48           | 1.08-2.04 | .015*   |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

In ALSPAC, there were no significant unadjusted associations in males between any birth anthropometric indices and cognitive outcomes (Table 7.14). After full adjustment, there was one significant association between BW<10<sup>th</sup> MGRS and poorer cognitive outcomes. In females, there were no significant unadjusted associations between any birth anthropometric indices and cognitive outcomes (Table 7.15). After full adjustment, significant associations were revealed for one index of wasting (PI-for-age<10<sup>th</sup> percentile) and two indices of asymmetry (HC/PI>90<sup>th</sup> percentile and HC/BMI>90<sup>th</sup> percentile). Thus there was one significant fully adjusted association between birth anthropometric indices and poorer cognitive outcomes in males, compared to three in females. The strongest associations were found for BW<10<sup>th</sup> MGRS in males (OR=2.15,  $p=.015$ ) and HC/PI>90<sup>th</sup> percentile in females (OR=2.30,  $p=.022$ ).

**Table 7.14. Unadjusted and adjusted associations between birth anthropometric indices and lower cognitive score in childhood in ALSPAC in males**

| Variables                                | Unadjusted |           |          | Fully adjusted |            |          |
|------------------------------------------|------------|-----------|----------|----------------|------------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI      | <i>p</i> |
| <b>Birth weight indices</b>              |            |           |          |                |            |          |
| BW <2500g                                | 1.17       | 0.49-2.78 | .723     | 1.32           | 0.50-3.46  | .575     |
| SGA                                      | 1.20       | 0.68-2.10 | .526     | 1.64           | 0.87-3.08  | .125     |
| BW <10 <sup>th</sup> MGRS                | 1.53       | 0.90-2.59 | .116     | 2.15           | 1.16-4.00  | .015*    |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.25       | 0.62-2.52 | .530     | 2.13           | 0.96-4.72  | .062     |
| <b>Stunting indices</b>                  |            |           |          |                |            |          |
| BL < 10 <sup>th</sup> MGRS               | 1.29       | 0.96-2.41 | .425     | 1.73           | 0.79-3.77  | .171     |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.33       | 0.53-3.34 | .541     | 1.93           | 0.58-6.36  | .283     |
| HC <10 <sup>th</sup> MGRS                | 1.63       | 0.77-3.47 | .205     | 2.83           | 0.98-8.19  | .056     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.32       | 0.68-7.91 | .179     | 4.39           | 0.88-21.97 | .072     |
| <b>Wasting indices</b>                   |            |           |          |                |            |          |
| PI <10 <sup>th</sup> percentile          | 0.98       | 0.62-1.55 | .933     | 0.92           | 0.52-1.61  | .767     |
| PI-for-age <10 <sup>th</sup> percentile  | 0.86       | 0.54-1.36 | .517     | 0.84           | 0.47-1.48  | .541     |
| BMI <10 <sup>th</sup> percentile         | 1.15       | 0.70-1.87 | .587     | 1.27           | 0.70-2.29  | .427     |
| BMI-for-age <10 <sup>th</sup> percentile | 0.97       | 0.58-1.61 | .904     | 1.30           | 0.70-2.42  | .410     |
| <b>Asymmetry indices</b>                 |            |           |          |                |            |          |
| HC/BL >90 <sup>th</sup> percentile       | 0.92       | 0.48-1.78 | .814     | 0.81           | 0.36-1.79  | .592     |
| HC/PI >90 <sup>th</sup> percentile       | 0.88       | 0.57-1.37 | .575     | 0.78           | 0.45-1.33  | .359     |
| HC/BMI >90 <sup>th</sup> percentile      | 0.96       | 0.60-1.53 | .855     | 1.02           | 0.58-1.79  | .940     |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

**Table 7.15. Unadjusted and adjusted associations between birth anthropometric indices and lower cognitive score in childhood in ALSPAC in females**

| Variables                                | Unadjusted |           |          | Fully adjusted |           |          |
|------------------------------------------|------------|-----------|----------|----------------|-----------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI     | <i>p</i> |
| <b>Birth weight indices</b>              |            |           |          |                |           |          |
| BW <2500g                                | 1.11       | 0.43-2.84 | .830     | 1.40           | 0.48-4.06 | .534     |
| SGA                                      | 1.05       | 0.52-2.14 | .980     | 0.92           | 0.39-2.17 | .851     |
| BW <10 <sup>th</sup> MGRS                | 1.08       | 0.54-2.19 | .822     | 1.43           | 0.60-3.38 | .421     |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.55       | 0.67-3.62 | .307     | 1.81           | 0.63-5.20 | .272     |
| <b>Stunting indices</b>                  |            |           |          |                |           |          |
| BL < 10 <sup>th</sup> MGRS               | 1.48       | 0.60-3.66 | .398     | 1.62           | 0.58-4.57 | .361     |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.38       | 0.85-6.64 | .099     | 1.67           | 0.48-5.80 | .416     |
| HC <10 <sup>th</sup> MGRS                | 1.20       | 0.51-2.84 | .676     | 1.54           | 0.58-4.08 | .383     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.01       | 0.72-5.60 | .182     | 2.78           | 0.94-8.26 | .065     |
| <b>Wasting indices</b>                   |            |           |          |                |           |          |
| PI <10 <sup>th</sup> percentile          | 1.22       | 0.68-2.16 | .505     | 1.82           | 0.95-3.47 | .071     |
| PI-for-age <10 <sup>th</sup> percentile  | 1.18       | 0.66-2.10 | .571     | 1.99           | 1.02-3.88 | .045*    |
| BMI <10 <sup>th</sup> percentile         | 0.89       | 0.51-1.56 | .690     | 1.13           | 0.59-2.13 | .718     |
| BMI-for-age <10 <sup>th</sup> percentile | 0.90       | 0.50-1.61 | .713     | 1.20           | 0.61-2.37 | .599     |
| <b>Asymmetry indices</b>                 |            |           |          |                |           |          |
| HC/BL >90 <sup>th</sup> percentile       | 1.08       | 0.55-2.10 | .830     | 0.97           | 0.44-2.16 | .942     |
| HC/PI >90 <sup>th</sup> percentile       | 1.14       | 0.61-2.16 | .677     | 2.30           | 1.13-4.71 | .022*    |
| HC/BMI >90 <sup>th</sup> percentile      | 1.09       | 0.59-2.00 | .779     | 2.05           | 1.00-4.22 | .049*    |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age



In INTERGROWTH-21<sup>st</sup>, there was one significant unadjusted association in males between an index of asymmetry (HC/BMI>90<sup>th</sup> percentile) and poorer cognitive outcomes (Table 7.16). This association did not remain significant, however, after full adjustment. In females, there were no significant associations between any birth anthropometric indices and cognitive outcomes for either unadjusted or fully adjusted associations (Table 7.17). Thus, there were no significant fully adjusted associations for males or females. A supplementary analysis was conducted to examine sex differences across INTERGROWTH-21<sup>st</sup> sites (Table S7.3). When separated by site there was no clear difference between sexes in associations between birth anthropometric indices and poorer cognitive outcomes. In some sites there were more associations for males (UK, Italy and India) whereas in others there were more associations for females (Brazil and Kenya).

**Table 7.16. Unadjusted and adjusted associations between birth anthropometric indices and lower cognitive score in childhood for INTERGROWTH-21st in males**

| Variables                                | Unadjusted |           |       | Fully adjusted |           |      |
|------------------------------------------|------------|-----------|-------|----------------|-----------|------|
|                                          | OR         | 95%CI     | p     | OR             | 95%CI     | p    |
| <b>Birth weight indices</b>              |            |           |       |                |           |      |
| BW <2500g                                | 1.12       | 0.51-2.49 | .776  | 0.85           | 0.33-2.19 | .740 |
| SGA                                      | 0.96       | 0.63-1.46 | .836  | 0.88           | 0.60-1.38 | .576 |
| BW <10 <sup>th</sup> MGRS                | 1.01       | 0.65-1.57 | .961  | 0.85           | 0.51-1.44 | .553 |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.36       | 0.81-2.26 | .246  | 1.21           | 0.71-2.09 | .484 |
| <b>Stunting indices</b>                  |            |           |       |                |           |      |
| BL < 10 <sup>th</sup> MGRS               | 0.83       | 0.52-1.34 | .443  | 0.68           | 0.39-1.17 | .164 |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.90       | 0.52-1.55 | .699  | 0.80           | 0.45-1.43 | .456 |
| HC <10 <sup>th</sup> MGRS                | 1.02       | 0.62-1.67 | .950  | 0.83           | 0.46-1.50 | .523 |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.92       | 0.46-1.83 | .814  | 0.78           | 0.38-1.61 | .506 |
| <b>Wasting indices</b>                   |            |           |       |                |           |      |
| PI <10 <sup>th</sup> percentile          | 1.65       | 0.96-2.86 | .072  | 1.44           | 0.80-2.58 | .221 |
| PI-for-age <10 <sup>th</sup> percentile  | 1.65       | 0.97-2.81 | .064  | 1.53           | 0.86-2.70 | .145 |
| BMI <10 <sup>th</sup> percentile         | 1.55       | 0.90-2.67 | .112  | 1.34           | 0.72-2.49 | .364 |
| BMI-for-age <10 <sup>th</sup> percentile | 1.28       | 0.76-2.14 | .351  | 1.08           | 0.62-1.89 | .784 |
| <b>Asymmetry indices</b>                 |            |           |       |                |           |      |
| HC/BL >90 <sup>th</sup> percentile       | 1.24       | 0.75-2.05 | .400  | 1.27           | 0.74-2.18 | .395 |
| HC/PI >90 <sup>th</sup> percentile       | 1.64       | 0.99-2.69 | .053  | 1.31           | 0.77-2.23 | .320 |
| HC/BMI >90 <sup>th</sup> percentile      | 1.81       | 1.04-3.16 | .036* | 1.48           | 0.81-2.71 | .205 |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

**Table 7.17. Unadjusted and adjusted associations between birth anthropometric indices and lower cognitive score in childhood for INTERGROWTH-21st in females**

| Variables                                | Unadjusted |           |          | Fully adjusted |           |          |
|------------------------------------------|------------|-----------|----------|----------------|-----------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI     | <i>p</i> |
| <b>Birth weight indices</b>              |            |           |          |                |           |          |
| BW <2500g                                | 0.71       | 0.40-1.28 | .258     | 0.68           | 0.35-1.33 | .260     |
| SGA                                      | 0.96       | 0.66-1.38 | .812     | 1.03           | 0.70-1.53 | .866     |
| BW <10 <sup>th</sup> MGRS                | 0.88       | 0.59-1.33 | .549     | 0.92           | 0.57-1.50 | .740     |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.96       | 0.61-1.54 | .878     | 1.03           | 0.63-1.71 | .896     |
| <b>Stunting indices</b>                  |            |           |          |                |           |          |
| BL < 10 <sup>th</sup> MGRS               | 0.70       | 0.45-1.11 | .131     | 0.68           | 0.41-1.13 | .133     |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.98       | 0.60-1.63 | .950     | 1.01           | 0.59-1.74 | .974     |
| HC <10 <sup>th</sup> MGRS                | 1.13       | 0.72-1.77 | .595     | 1.24           | 0.74-2.09 | .414     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.26       | 0.69-2.32 | .452     | 1.32           | 0.70-2.48 | .396     |
| <b>Wasting indices</b>                   |            |           |          |                |           |          |
| PI <10 <sup>th</sup> percentile          | 1.07       | 0.61-1.86 | .819     | 1.23           | 0.68-2.23 | .495     |
| PI-for-age <10 <sup>th</sup> percentile  | 1.24       | 0.72-2.14 | .442     | 1.45           | 0.81-2.58 | .209     |
| BMI <10 <sup>th</sup> percentile         | 1.36       | 0.79-2.34 | .262     | 1.58           | 0.87-2.89 | .134     |
| BMI-for-age <10 <sup>th</sup> percentile | 1.18       | 0.69-2.02 | .539     | 1.26           | 0.73-2.20 | .411     |
| <b>Asymmetry indices</b>                 |            |           |          |                |           |          |
| HC/BL >90 <sup>th</sup> percentile       | 0.67       | 0.39-1.15 | .145     | 0.61           | 0.34-1.10 | .098     |
| HC/PI >90 <sup>th</sup> percentile       | 1.00       | 0.55-1.82 | .990     | 1.21           | 0.64-2.29 | .565     |
| HC/BMI >90 <sup>th</sup> percentile      | 0.67       | 0.38-1.18 | .163     | 0.79           | 0.43-1.45 | .438     |

OR>1=poorer outcome; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

Table 7.18 shows the direction and statistical significance of associations across all three cohorts. Overall there were a similar number of associations with birth anthropometric indices and cognitive outcomes for males (12 across cohorts) and females (13 across cohorts). Furthermore, cohorts differed in which birth anthropometric indices were most strongly associated with cognitive outcomes in males and females. For males, the strongest association was with an index of stunting in Pelotas (HC <10<sup>th</sup> percentile MGRS), and with an index of BW in ALSPAC (BW <10<sup>th</sup> percentile MGRS; OR range = 1.80-2.15). For females, the strongest association was between an index of stunting in Pelotas (HC <10<sup>th</sup> percentile MGRS) and an index of asymmetry in ALSPAC (HC/PI >90<sup>th</sup> percentile; OR range = 1.91-2.30) and poorer cognitive outcomes.

**Table 7.18. Significant adjusted associations between birth anthropometric indices and lower cognitive scores in Pelotas, ALSPAC and INTERGROWTH-21st in males and females**

| Variable                                 | Males   |        |        | Females |        |        |
|------------------------------------------|---------|--------|--------|---------|--------|--------|
|                                          | Pelotas | ALSPAC | I-21st | Pelotas | ALSPAC | I-21st |
| <b>BW indices</b>                        |         |        |        |         |        |        |
| BW <2500g                                | +       | +      | -      | +       | +      | -      |
| SGA                                      | +       | +      | -      | +       | -      | +      |
| BW <10 <sup>th</sup> MGRS                | +       | +      | -      | +       | +      | -      |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | +       | +      | +      | +       | +      | +      |
| <b>Stunting indices</b>                  |         |        |        |         |        |        |
| BL <10 <sup>th</sup> MGRS                | +       | +      | -      | +       | +      | -      |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | +       | +      | -      | +       | +      | +      |
| HC <10 <sup>th</sup> MGRS                | +       | +      | -      | +       | +      | +      |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | +       | +      | -      | +       | +      | +      |
| <b>Wasting indices</b>                   |         |        |        |         |        |        |
| PI <10 <sup>th</sup> percentile          | +       | -      | +      | +       | +      | +      |
| PI-for-age <10 <sup>th</sup> percentile  | -       | -      | +      | +       | +      | +      |
| BMI <10 <sup>th</sup> percentile         | +       | +      | +      | +       | +      | +      |
| BMI-for-age <10 <sup>th</sup> percentile | +       | +      | +      | +       | +      | +      |
| <b>Asymmetry indices</b>                 |         |        |        |         |        |        |
| HC/BL >90 <sup>th</sup> percentile       | +       | -      | +      | +       | -      | -      |
| HC/PI >90 <sup>th</sup> percentile       | -       | -      | +      | +       | +      | +      |
| HC/BMI >90 <sup>th</sup> percentile      | +       | +      | +      | +       | +      | -      |

+ = OR > 1.00 (positive association); - = OR < 1.00 (negative association); OR > 1 = poorer outcome; \* = p < .05; \*\* = p < .001

### 7.3.5 Sensitivity, specificity and receiver-operating characteristic (ROC) analysis

Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for each of the birth anthropometric indices were assessed to compare the indices on predictive value separately for males and females. For attention, averaging across cohorts, indices of stunting were stronger predictors of poor attention outcomes (with overall better sensitivity, specificity, PPV and NPV) than BW, wasting or

asymmetry indices in both males and females (Tables S7.2-S7.7), with consistency across cohorts. The strongest stunting predictor was BL, which was a stronger predictor of poor attention outcomes in females than in males. For cognition, averaging across cohorts, indices of BW were stronger predictors of poor cognitive outcomes in males, and indices of wasting were stronger predictors in females (Tables S7.8-S7.13). There was little consistency across cohorts however, with the strongest predictors of poor cognitive outcomes in males being stunting in Pelotas, BW in ALSPAC and asymmetry in INTERGROWTH-21<sup>st</sup>, and in females, BW in Pelotas and wasting in ALSPAC and INTERGROWTH-21<sup>st</sup>. ROC curves are presented for attention and cognitive outcomes in Figures S7.1 and S7.2, respectively.

## **7.4 Summary of results**

The results of this chapter report differential effects of sex on the association between birth anthropometric indices and poorer attention outcomes, with stronger associations in females than in males. The strongest associations for females in all three cohorts were identified between indices of stunting and poorer attention outcomes. Furthermore, stunting (specifically BL) was also identified as the strongest predictor of poor attention outcomes, with higher overall sensitivity and specificity. There were no clear differences identified between sexes in associations between birth anthropometric indices and cognitive development.

### **7.4.1 How this chapter builds on previous chapters**

The results of the current chapter nuance the results of Chapters 5 and 6. Chapter 5 showed that stunting (specifically BL) was significantly associated with poorer attention outcomes in the Pelotas and ALSPAC cohorts, and was the strongest predictor of poor attention outcomes in all three cohorts. The results of the current analysis suggest that these associations are moderated by sex, such that they are stronger in females. Furthermore, a significant association for stunting (BL) and poorer attention outcomes was also revealed in the INTERGROWTH-21<sup>st</sup> cohort in females only. Analysis of sex differences by INTERGROWTH-21<sup>st</sup> site

built on the findings of Chapter 6, and showed that a specific effect for females was present across high-, middle- and low-income countries. This extended the findings of Chapter 6, which had identified associations between BL and poorer attention outcomes only in samples from higher-income countries. The results of the current chapter revealed that when separated by sex, an association between BL and poorer attention outcomes was also revealed in a sample from Kenya, a low-income country.

## **7.5 Conclusions**

In conclusion, this chapter identified sex as a moderator in the associations between birth anthropometric indices and attention outcomes. The association between stunting and poorer attention outcomes appears to be stronger in females, and this pattern is evident in samples from high-, middle- and low-income countries. There were no sex differences identified in associations between birth anthropometric indices and cognitive outcomes, suggesting that sex moderation may be domain-specific (i.e. affecting attention but not cognitive development).

## 7.6 References

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## 8 General discussion

### Chapter outline

#### 8.1 Summary of thesis

#### 8.2 Discussion of the results of the systematic review

#### 8.3 Comparisons of indices of fetal growth as predictors of attention and cognitive development

8.3.1. Birth weight as a predictor of attention and cognitive development

8.3.2 Stunting as a predictor of attention and cognitive development

8.3.3 Wasting as a predictor of attention and cognitive development

8.3.4 Asymmetry as a predictor of attention and cognitive development

8.3.5 Age at assessment

8.3.6 Sensitivity vs specificity

#### 8.4 Differences in associations between growth references and growth standards

#### 8.5 Potential neural mechanisms linking fetal growth to attention and cognitive development

8.5.1 Potential neural mechanisms linking fetal growth, attention and cognition to other neurodevelopmental impairments

8.5.2 Potential mechanisms underlying the effect of fetal circulatory redistribution

#### 8.6 Sex-specific differences in the association between fetal growth and attention development

8.6.1 Evidence of female-specific vulnerability to impaired fetal growth

#### 8.7 Differences between high-, middle- and low-income countries

#### 8.8 Methodological strengths and limitations

8.8.1 Original contributions

8.8.2 Strengths of methodology

8.8.3 Limitations of methodology

#### 8.9 Implications of findings for policy, clinical practice and research

8.9.1 Policy implications

8.9.2 Clinical practice implications

8.9.3 Research implications

#### 8.10 Conclusions

#### 8.11 References

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## 8.1 Summary of thesis

The overarching objective of this thesis was to examine the association between impaired fetal growth, using a range of indices measured at birth, and attention and cognitive outcomes in childhood. This over-arching objective was divided into five specific sub-aims: (1) to examine association between fetal growth impairment and neurodevelopment in childhood, by conducting a systematic review of the literature using a stringent definition of fetal growth impairment; (2) to conduct a validation of the INTER-NDA, a neurodevelopmental assessment tool to assess neurodevelopment at age 2 years, against a current 'gold standard' infant neurodevelopmental assessment; (3) to examine the associations between a range of different indices of impaired fetal growth measured at birth (including BW, stunting, wasting and asymmetry at birth) and attention and cognitive development in childhood; (4) to examine whether the associations between birth anthropometric indices and attention and cognitive development differ between high-, upper-middle-, lower-middle and low-income countries; and (5) to examine whether the associations between birth anthropometric indices and attention and cognitive development are moderated by sex.

The results chapters of this thesis have addressed each aim in turn, to develop a clearer understanding of the association between impaired fetal growth (specifically when identified by birth anthropometric indices) and attention and cognitive development in childhood. The results of Chapter 2, a systematic review of the literature, showed that impaired fetal growth is associated with poor neurodevelopmental outcomes in childhood, particularly attention and cognitive development. Chapter 3 laid out the methodology for the remainder of the thesis, which would compare the associations between impaired fetal growth, measured at birth, and attention and cognitive outcomes in three cohorts (Pelotas, ALSAC and INTERGROWTH-21<sup>st</sup>). The results of Chapter 4 showed that the INTER-NDA is a valid tool for assessing neurodevelopment at two years of age, which was then used in Chapters 5, 6 and 7 as a measure of infant attention and cognition in the INTERGROWTH-21<sup>st</sup> cohort. The results of Chapter 5

showed that associations differed between birth anthropometric indices and attention and cognitive outcomes in childhood, with stunting (BL) associated with attention impairment, and both stunting (HC) and wasting associated with cognitive impairment. These were small, but significant effects. The results of Chapter 6 showed that the associations of BL with attention outcomes were more evident in higher-income countries, whereas the associations of HC and wasting with cognitive outcomes were more evident in lower-income countries. The results of this chapter also showed that maternal 'low-risk' status may provide some protection against poor attention and cognitive outcomes associated with impaired fetal growth. The results of Chapter 7 showed that the associations between BL and attention outcomes were markedly stronger in females, and that in females, associations between BL and attention outcomes were also evident in low-income samples. There were no sex differences identified in the associations between birth anthropometric indices and later cognitive development. The contribution of each results chapter is summarised in Table 8.1.

**Table 8.1. Overview of thesis findings by results chapters**

|                  | <b>Chap 2</b><br><b>Systematic review</b>                          | <b>Chap 4</b><br><b>Validation of assessments</b>            | <b>Chap 5</b><br><b>Strongest associations</b> | <b>Chap 6</b><br><b>Differences between HIC, MIC and LIC populations in associations</b>                   | <b>Chap 7</b><br><b>Sex-specific effects in the association between fetal growth impairment and attention/cognitive outcomes</b> |
|------------------|--------------------------------------------------------------------|--------------------------------------------------------------|------------------------------------------------|------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| <b>Attention</b> | Fetal growth impairment is associated with poor attention outcomes | INTER-NDA shown to be a valid assessment of infant cognition | Stunting (BL)                                  | Associations between stunting and attention outcomes predominantly in higher-income countries <sup>a</sup> | Markedly stronger in females                                                                                                     |
| <b>Cognition</b> | Fetal growth impairment is associated with poor cognitive outcomes | INTER-NDA shown to be a valid assessment of infant cognition | Stunting (HC) and wasting                      | Associations between stunting and wasting and cognitive outcomes predominantly in lower-income countries   | Similar in both sexes                                                                                                            |

<sup>a</sup> Also in low-income country when including only females in the analysis; BL = birth length; BW = birth weight; HC = head circumference; CBCL = Child Behaviour Checklist; CBQ = Child Behaviour Questionnaire; INTER-NDA = INTERGROWTH-21<sup>st</sup> Neurodevelopment Assessment; SDQ = Strengths and Difficulties Questionnaire; WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence - Revised

## 8.2 Discussion of the results of the systematic review

The aim of the systematic review was to examine the association between fetal growth impairment and neurodevelopment in childhood. The results of the systematic review were used to inform the research focus for the remainder of the thesis. Fetal growth impairment was prospectively identified using in utero measures, and confirmed by anthropometric indices at birth. Neurodevelopment was assessed across a number of domains, up to twelve years of age, including behaviour, cognition, language, motor, vision, hearing and sleep. The results showed a nuanced pattern of effects across neurodevelopmental domain. Fetal growth impairment was most consistently associated with poorer cognitive and behaviour (specifically attention) outcomes in childhood.

The finding of varied effects of fetal growth impairment across neurodevelopment domains suggests domain-specific effects of growth, as opposed to global effects of growth on *overall* neurodevelopment. This differential pattern has also been identified in previous research on the neurodevelopmental effects of fetal growth measures taken at birth, including LBW, SGA and HC<sup>1-3</sup>. Such varied neurodevelopmental outcomes may arise from different effects of intrauterine insults on the neural development of the fetus<sup>4</sup>. The effect of intrauterine insults on neural development may related to the timing, duration and severity of insult.

Timing, duration and severity of intrauterine insult also affects the growth phenotype of the developing fetus<sup>5</sup> (i.e. whether growth impairment manifests as stunting or wasting at birth). Fetal growth impairment confirmed by stunting or wasting at birth was associated with more negative neurodevelopmental outcomes, compared to fetal growth impairment confirmed by BW indices. Fetal circulatory redistribution (FCR), which can be indicated by growth asymmetry at birth<sup>6</sup>, discussed in detail in Chapter 1, was also associated with an increased risk of neurodevelopmental impairment. The potential mechanisms underpinning the

association between fetal growth impairment and neurodevelopment will be further discussed in section 8.5.

Few of the studies (10%) examined sex-specific effects, and those that did showed mixed results. All the studies were conducted in high-income countries (HICs), with the exception of one study from Jamaica<sup>7</sup> (an upper-middle income country), confirming the over-reliance on data from HICs.

The findings of the systematic review suggest that fetal growth impairment is associated with greater effects on neurodevelopment than has been indicated by a previous review by Arcangeli et al. (2012). The review by Arcangeli et al., identified fetal growth impairment retrospectively at birth, using BW measures<sup>8</sup>. It reported an approximate impairment of 0.3 SD. In comparison, the current systematic review, which used a more stringent method of classification of fetal growth impairment, identified an approximate impairment of 0.5 SD in those born  $\geq 35$  weeks, and 0.7 SD in those born  $< 35$  weeks.

The findings from the systematic review informed the design and methodology for the thesis in the following ways: (1) attention and cognition were examined as the neurodevelopmental outcomes of interest; (2) fetal growth impairment at birth was divided into birth anthropometric indices of BW, stunting, wasting and asymmetry, based on the birth measurements used in previous studies and potential effects of FCR (Chapter 5); (3) a separate follow-up analysis was conducted examining potential differences across samples from high-, middle- and low-income countries (Chapter 6); (4) a separate analysis of effects separated by sex was conducted (Chapter 7); and (5) all analyses accounted for difference in GA at birth. The results of these analyses are discussed below.

### **8.3 Comparison of indices of fetal growth impairment as predictors of attention and cognitive development in childhood**

One of the primary aims of this thesis was to identify whether some indices of impaired fetal growth would better predictors of attention and cognitive outcomes in childhood than others. This question was addressed across Chapters 5, 6 and 7, the results of which are synthesised below. Birth anthropometric indices were divided into broad categories of BW, stunting, wasting and asymmetry. This division was based on previous research that had identified (a) differential effects of BW, stunting and wasting in childhood on neurodevelopment<sup>9</sup>, and (b) differential effects of BW, stunting and wasting at birth on neonatal prognoses<sup>5</sup>. There has been little examination of the effects of indices of asymmetry at birth, as such, these analyses were included as exploratory. The attention system measured was that of endogenous attention, assessed by parental-report (using the CBCL and SDQ). Endogenous attention reflects readily observable constructs of attention such as attention span, distractibility and persistence. Cognitive outcomes were measured using cognitive assessments (the WPPSI-R and the INTER-NDA) designed to test infant and child cognitive abilities.

#### **8.3.1 Birth weight as a predictor of attention and cognitive development in childhood**

This thesis examined four BW indices including LBW (<2500g), small-for-gestational age (SGA) by the US National Fetal Growth Reference<sup>10</sup>, BW less than 10<sup>th</sup> percentile for sex by MGRS standards, and BW less than 10<sup>th</sup> percentile for gestational age (GA) and sex by INTERGROWTH-21<sup>st</sup> standards. The results showed that BW indices were poorer predictors of attention and cognitive outcomes compared to indices of stunting and wasting. This is in support of recent research which has suggested that as BW is an inferior indicator of fetal growth processes than stunting and wasting<sup>5</sup>. This finding supports calls for clinical practice to move away from indices of BW as an assessment of fetal growth<sup>5</sup>.

### **8.3.2 Stunting as a predictor of attention and cognitive development in childhood**

This thesis examined four stunting indices, including MGRS and INTERGROWTH-21<sup>st</sup> standards for both BL and HC. BL and HC are skeletal measurements, which are not affected by variations in neonatal adipose tissue<sup>11</sup>. These measurements were shown to be differentially associated with attention and cognitive outcomes. BL was markedly associated with poorer attention outcomes, which was consistently identified in analyses across all three cohorts. This effect appeared particularly strong in females. For cognitive outcomes, HC was the strongest predictor, identified across all three cohorts by sensitivity and specificity analyses.

The association between BL and attention impairment in childhood has been reported in a number of previous studies<sup>12,13</sup>. Stunted BL is thought to arise from slow skeletal growth sustained over time<sup>11</sup>. This is usually the result of a chronic intrauterine insult, arising from a number of risk factors sustained throughout pregnancy, rather than an acute environmental disturbance.

This sustained disturbance in prenatal growth may have particular consequences for attention development. Recent reviews have shown that poor pre- and postnatal growth may increase the risk of attention problems in childhood<sup>14,15</sup>. Furthermore, a longitudinal study of length/height over time showed that BL was more strongly associated with ADHD symptoms at 4.5 years of age, than measurements of length/height or growth in childhood<sup>12</sup>. The results of this thesis support previous findings, and emphasise the specific importance of sustained skeletal growth in the prenatal period, for the healthy development of attention<sup>12</sup>. Given the higher prevalence of stunting in LMICs, this finding has important implications for the ability of children in LMICs to reach their developmental potential.

Whereas BL was consistently associated with attention development, HC was more strongly associated with cognitive development. These findings replicate a previous study which found that HC was associated with cognitive, but not attention, outcomes in childhood<sup>16</sup>. The



physiology underpinning this association may be brain volume. HC has been shown to be strongly correlated with total brain volume ( $r=0.93$ ), and thus provides an accurate, rapid, and inexpensive indication of brain size<sup>17</sup>. A number of studies have identified an association between HC and cognitive development in childhood<sup>18,19</sup>. Furthermore, the importance of HC growth in the *fetal* period has been particularly emphasised. A study by Gale et al. (2006)<sup>19</sup> examined the effects of HC size at birth, compared to in the postnatal and childhood period, on cognitive function at 4 years of age. This study identified restricted HC at birth to be more strongly associated with cognitive impairment compared to other developmental periods.

### **8.3.3 Wasting as a predictor of attention and cognitive development in childhood**

In this thesis, four indices of wasting were examined, including  $PI < 10^{\text{th}}$  percentile,  $BMI < 10^{\text{th}}$  percentile,  $PI\text{-for-GA} < 10^{\text{th}}$  percentile and  $BMI\text{-for-GA} < 10^{\text{th}}$  percentile. Two patterns were identified across the three cohorts: (1) indices of wasting were associated with cognitive but not attention impairment, and (2) associations were identified in LMICs, but not in HICs. This result may be explained by the fact that wasting is more common in LMICs than in HICs, with 75% of wasted children living in Asia<sup>20</sup>. Comparing the prevalence of wasting indices across INTERGROWTH-21<sup>st</sup> sites, the results of the current study support this trend. For example, the prevalence of neonates falling below the 10<sup>th</sup> percentile for PI in the INTERGROWTH-21<sup>st</sup> sample was 22.7% in India, compared to 2.9% in the UK. Although it is possible that higher prevalence increases the power to detect associations in LMICs, associations between wasting and cognitive outcomes were also identified in the Pelotas 2004 but not the ALSPAC cohort, despite greater power in the ALSPAC cohort.

The strongest wasting predictor of cognitive impairment was PI below the 10<sup>th</sup> percentile. PI has been previously shown to be associated with cognitive development in LMIC samples from China<sup>21</sup> and Guatemala<sup>4</sup>. Conversely, the vast majority of studies in HICs have shown no significant associations between wasting and cognitive outcomes, including samples

from Australia<sup>22</sup>, Norway and Sweden<sup>23</sup>, France<sup>24</sup> and the USA<sup>25</sup>. This suggests that there may be specific factors in LMICs (such as different confounding structures) underpinning the association between wasting and cognitive impairment. Differences in associations between lower- and higher-income countries will be further discussed in section 8.7.

#### **8.3.4 Asymmetry as a predictor of attention and cognitive development in childhood**

The current thesis included three ratio indices, HC/BL, HC/PI and HC/BMI, to explore the potential association between growth asymmetry with attention and cognitive outcomes. Ratios of HC to other birth anthropometric measurements may reflect FCR processes during fetal development, which usually occur in the last trimester<sup>26</sup>. Negative outcomes of growth asymmetry have been explored in previous research including HC/BL<sup>27</sup>, waist/hip and waist/height<sup>28</sup>, femur length/abdominal circumference (AC)<sup>29</sup>, mid-arm circumference/HC<sup>30</sup> and HC/AC<sup>31</sup>, with mixed results. The results of the current thesis showed only a small number of significant associations, with small effect sizes and inconsistent results across cohorts.

Chapters 5 (Table 5.6) and 6 revealed an unadjusted association between an elevated HC/BL in the Pelotas birth cohort, and in the Kenyan site of the INTERGROWTH-21<sup>st</sup> cohort (Table 6.5), and poorer attention outcomes. A high HC/BL ratio has been shown to result from maternal undernutrition<sup>32</sup>. One study, however, showed that a *low* HC/BL ratio (i.e. restricted HC relative to BL) was associated with behavioural symptoms of ADHD<sup>27</sup>. This study also showed an association with HC alone, suggesting that an overall restricted HC might be underpin this association.

An elevated HC/BMI ratio (above 90<sup>th</sup> percentile) was associated with attention and cognitive impairment in the Pelotas birth cohort (Table 5.6; Table 5.10). Whilst the association with cognition remained present after adjusting for maternal, demographic, perinatal, gestational and childhood factors, the association with attention did not. HC/BMI provides an

indicator of HC to adiposity. An elevated HC/BMI may reflect FCR, specifically preferential perfusion of the fetal brain at the expense of other downstream organs. These circulatory adaptations most commonly arise in the presence of placental insufficiency<sup>6</sup>. Such processes may lead to a growth impaired phenotype with a reduced BMI, but a relatively 'preserved' HC.

Whilst there have been no studies examining the HC/BMI ratio, some studies have examined the HC/AC ratio. Similar to HC/BMI, HC/AC provides an indicator of HC to abdominal adiposity. A significant moderate association has been identified between PI and AC ( $r=0.40$ )<sup>33</sup>, suggesting that in the absence of AC data, other adiposity measures may provide an adequate correlate. An elevated HC/AC ratio has been shown to be associated with increased neonatal morbidity<sup>34</sup> and poorer pregnancy outcomes<sup>35</sup>. Furthermore, research into the neurodevelopmental outcomes of an elevated HC/AC ratio at birth in the 2004 Pelotas birth cohort<sup>31</sup>, found a significant association between a high HC/AC ratio and attention impairment in females, after adjusting for maternal, demographic and gestational variables.

Overall, the results of the exploratory asymmetry analyses suggest that there may be some small effects of asymmetric growth on attention and cognitive development. The asymmetric growth phenotypes (such as an elevated HC/BMI) may provide some insight into the processes leading to fetal growth impairment. Asymmetry indices, however, are not as useful as other anthropometric indicators (i.e. BL for attention, and HC or PI for cognition) for identifying children at risk of neurodevelopmental impairment. As such, asymmetry indices may provide supplementary information about the risk of poorer neurodevelopmental outcomes, however should be used in conjunction with other indicators of impaired fetal growth.

### **8.3.5 Age at assessment**

This thesis included neurodevelopmental assessments carried out on infants and children between the ages of 2 and 6 years of age. The systematic review identified that the negative effect of fetal growth impairment on cognitive outcome became more pronounced as

children grew older, as identified in the graphical depiction of standardised mean difference (the difference between groups, expressed as SD) across postnatal age. No cognitive effects were identified before 18 months of age. Similarly, the results of the current thesis identified stronger associations between indices of fetal growth, taken at birth, and cognitive outcomes at ages 4 and 6, compared to age 2. These findings must be interpreted with caution however, as these differences were identified between cohorts, rather than within the same group of children measured repeatedly.

This finding of strengthening associations as children age is in support of studies that have identified no clinical difference in early cognitive ability between SGA and control children, but later identified SGA children to be in need of additional educational support<sup>36</sup>. A similar pattern has been identified in the effects of lead, whereby cognitive impairment becomes more apparent as children age<sup>37</sup>. This increasing impairment has been termed a 'sleeping effect' in child development<sup>38</sup>, and refers to a situation in which an association, which may not be initially identifiable, becomes stronger as a child ages. A possible explanation for this effect observed in cognitive outcomes in the systematic review may be that cognitive effects are due to underlying deficits in executive function, which develops later in childhood. Executive function (can be observed and measured from 3 years of age onwards, develops rapidly between 7 years and 10 years<sup>39</sup>, and continues sequentially until adolescence<sup>40</sup>). An alternative explanation is that the narrow range of skills at a young age does not permit a nuanced assessment of neurodevelopmental abilities, whereas at older ages, assessment measures are better able to identify task-specific impairments.

### **8.3.6 Sensitivity vs specificity**

In order to obtain an indicator of the extent to which the different growth measures at birth predicted later attention and cognitive development, sensitivity and specificity analyses were undertaken. Overall, sensitivity and specificity analyses showed a similar pattern across all

growth indices: there was relatively low sensitivity, but high specificity. Sensitivity measures the proportion of those with impaired fetal growth at birth (<10<sup>th</sup> percentile) with poor neurodevelopmental outcomes, whereas specificity measures the proportion of those with unimpaired growth at birth ( $\geq 10^{\text{th}}$  percentile) whose neurodevelopmental outcomes will be in the normal range. Whether sensitivity or specificity is considered more important relates to the intended purposes of the indicator<sup>11</sup>. If an indicator is to be used as a diagnostic tool, sensitivity is more important to ensure a high number of correctly identified cases. If an indicator is to be used as a screening tool however, specificity may be more important to ensure a) that a higher number of children are screened; and b) that those that are 'missed' by the screening tool have a low likelihood of poor neurodevelopmental outcomes. In the case of the use of birth anthropometric indices as predictors of neurodevelopment, specificity may be considered a higher priority than sensitivity. The current thesis showed that, averaged across the three cohorts, BL had 90% specificity for attention outcomes, and HC and PI had 90% specificity for cognitive outcomes. This means that 90% of children identified as 'not at risk' using these indicators, will have neurodevelopment within the normal range in childhood.

#### **8.4 Differences in associations between growth references and growth standards**

The current thesis included the US National Fetal Growth Reference<sup>10</sup> as well as two growth standards (MGRS and INTERGROWTH-21<sup>st</sup>) to classify neonates with growth impairment. The results of the current thesis show that the percentage of growth restricted children by the US National Fetal Growth Reference was almost 40% in India, in comparison with 7.5% in the UK. This indicates that, as expected, the US reference may be over-estimating the prevalence of children born SGA in lower-income countries, and is thus of limited use in populations from LMICs<sup>11</sup>. Comparing the MGRS and INTERGROWTH-21<sup>st</sup> standards, more neonates were classified as growth restricted by MGRS standards than by INTERGROWTH-21<sup>st</sup> standards, on all indices of BW, BL and HC. For both BW and BL, the strongest associations with cognitive and attention impairment were mixed between MGRS and INTERGROWTH-21<sup>st</sup> standards, although

the INTERGROWTH-21<sup>st</sup> standards had superior predictive ability in sensitivity and specificity analyses. These findings require much further examination, however one explanation is that INTERGROWTH-21<sup>st</sup> standards of BW and BL may be superior for identifying children at risk of poorer attention and cognitive outcomes, as accounting for GA at birth more accurately distinguishes those who are growth impaired from those who are not.

### **8.5 Potential neural mechanisms linking fetal growth to attention and cognitive outcomes**

Attention and cognitive development were significantly moderately correlated in all three cohorts ( $r=.29$  in Pelotas,  $r=.29$  in ALSPAC and  $r=.35$  in INTERGROWTH-21<sup>st</sup>, all  $p<.001$ ). These outcomes, however, differed in the strength of associations with birth anthropometric indices. Two propositions may be made from this finding: a) that the neural mechanisms associated with attention and cognitive development may include different, but overlapping, regions or networks; and b) that different phenotypes of fetal growth impairment have specific effects on the developing nervous system<sup>41</sup>. These propositions are consistent with the current understanding of the development of attention and cognition in childhood, and the associated underlying neural mechanisms<sup>42</sup>.

Previous studies have identified a correlation between early measures of attention and both concurrent and later cognitive abilities<sup>43,44</sup>. Furthermore, the infant's ability to sustain attention and thus process information effectively, is one of the most robust predictors of IQ in later childhood<sup>45</sup>. Taken together, these findings suggest that there is significant overlap between attention and cognitive functions. Despite this, however, studies of attention in preterm children have shown that poor attention outcomes cannot be explained fully by general cognitive deficit<sup>46,47</sup>. This suggests that attention development may be specifically affected in preterm children.

There is also neural evidence for overlapping but separate mechanisms. Four ascending pathways, beginning at the brainstem, have been suggested to underpin attention function. These ascending pathways are generally characterized as independent entities, and identified by their predominant neurotransmitter (noradrenergic, cholinergic, serotonergic, and dopaminergic). The pathways share several common limbic and cortical targets, including frontal areas<sup>48</sup>. Two of the four ascending pathways (noradrenergic and cholinergic), appear to be especially involved in cognitive function<sup>49</sup>, providing a potential correlate for overlapping but different neural mechanisms underpinning attention and cognitive development.

Neurodevelopmental abilities follow different developmental trajectories throughout pre- and post-natal development, with some continuing to develop into adolescence<sup>50</sup>. Early attention development is guided by several underlying systems that emerge and function differently, at different points during development<sup>49</sup>. During the first year of life, four different functions of attention come online (alertness, spatial orienting, attention to object features and endogenous attention) and develop at separate points in time<sup>51</sup>. Most relevant to this thesis is the endogenous attention system, which refers to observable manifestations of attention, and is the construct identified by parental-report measures. Endogenous attention emerges toward the end of the first year of life, and continues to develop into early childhood<sup>52</sup>.

Developing neural systems undergo periods of accelerated development, which usually coincide with growth spurts in the developing brain<sup>53</sup>. Periods of accelerated growth have been referred to as 'sensitive periods' for structural and functional neural development<sup>41</sup>. Insult during a sensitive period of development may have specific effects on growth (leading to different growth phenotypes such as stunting or wasting<sup>4</sup>). Such insults may also have specific effects on the structure and function of the developing nervous system, and thus differential effects on neurodevelopment (Figure 8.1).

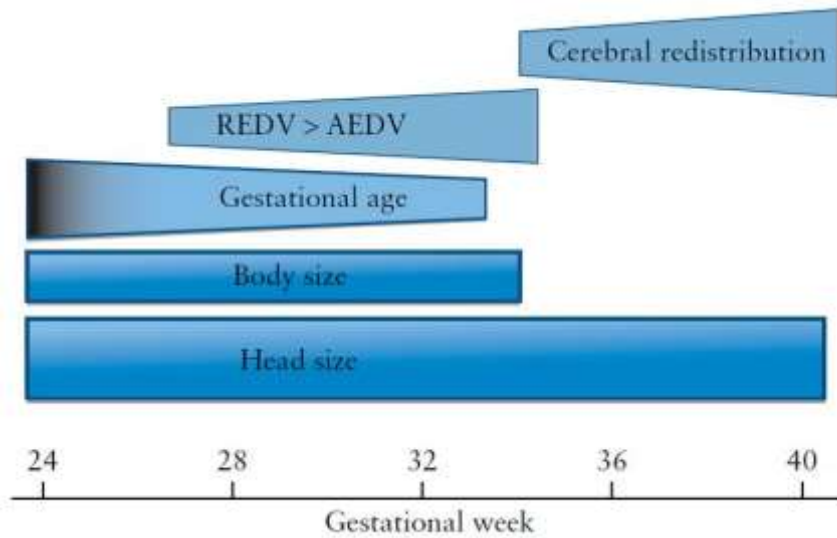


**Figure 8.1. Critical timing of growth impairment and growth-related factors associated with neurodevelopmental impairment, according to Baschat et al. (2011)<sup>54</sup>. Cerebral redistribution, Doppler parameters (reverse-end diastolic flow more than absent-end diastolic flow) gestational age at birth, body size (weight) at birth and head size (circumference) at birth all have critical windows in which insult has a greater effect on neurodevelopment, moderated by the duration and severity of the insult.**

Neurostructural changes arising from adverse intrauterine environments include both (a) global changes in neural structures and functions, and (b) region-specific changes<sup>41</sup>. As such, some growth phenotypes may be more associated with particular neurodevelopmental outcomes than others (due to varied effects on global and region-specific neural development). Growth phenotypes have been suggested to be determined by the timing, duration and severity of intrauterine insults<sup>4</sup>. As such, variation in the intrauterine milieu may have effects on both growth and neural development, leading to specific associations between particular growth phenotypes and neurodevelopmental outcomes. These suggested mechanisms are depicted in Figure 8.2. The current thesis provided evidence to support this theory by showing that different indices of growth impairment were differentially associated with neurodevelopmental



outcomes. Whereas restricted BL was most strongly associated with attention impairment, restricted HC and a low PI were most strongly associated with cognitive impairment.

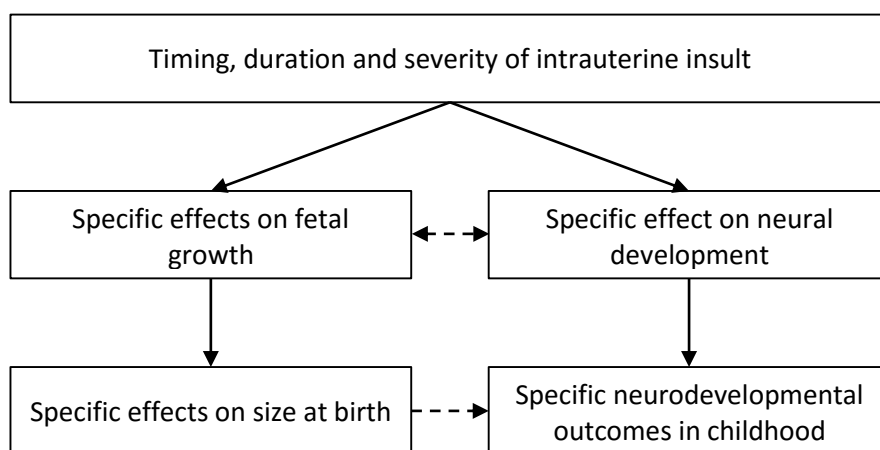


**Figure 8.2. Suggested mechanisms linking size at birth to neurodevelopmental outcomes in childhood**

The mechanism linking BL and poorer attention outcomes may be global neural disturbances (i.e. disturbances relating to the whole brain rather than region-specific) during fetal development. BL is affected by a combination of adverse factors sustained throughout fetal development, leading to global disturbance of skeletal growth. Gross disturbance of fetal growth has been associated with global effects on neural development, for example, reduced cortical thickness<sup>55</sup>. Reduced cortical thickness has been identified in children with attention problems compared to aged-matched controls<sup>56</sup> (Figure 8.3), which may be reflective of reduced dendritic arborisation and a reduction in grey matter volume across multiple neural systems. Both reduced dendritic arborisation<sup>57,58</sup> and a reduction in absolute grey matter have been identified

as sequelae of impaired fetal growth<sup>59,60</sup>. As such, global neural disturbances, such as cortical thinning in multiple neural systems, may be the mechanism underlying the association between restricted BL and poorer attention outcomes in childhood.

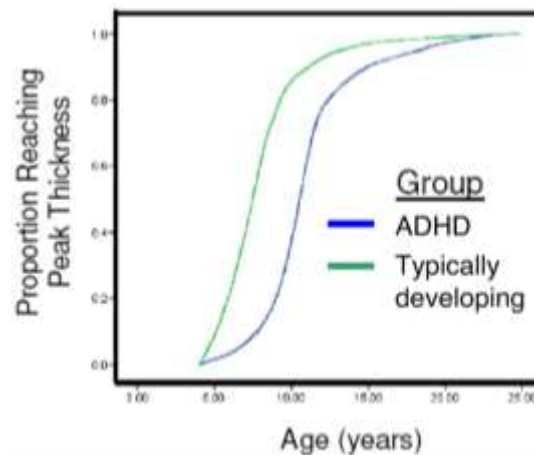


**Figure 8.3. The proportion of all cerebral points that attained peak cortical thickness by age, in children with ADHD and controls<sup>56</sup>**

By contrast, restricted HC and PI are more specific indicators of impaired fetal growth, arising from specific disturbances in the fetal growth process. These indices may be more likely to arise from insults in late gestation, a period of accelerated fetal brain growth<sup>61</sup> and increasing adiposity<sup>62</sup>. Small HC in the third trimester may be particularly associated with cognitive impairment due to disturbance in the development of neural structures and circuits<sup>63</sup> and overall brain volume<sup>3</sup>. A recent study identified a strong correlation between a small HC and brain volume at term<sup>3</sup> (Figure 8.4). In this study, reduction in brain volume tissue was associated with lower mental development index (MDI) but not performance development index (PDI) at two years on the BSID. The results of the systematic review (Chapter 2) supported this finding, showing that FCR had effects on cognitive, but not motor, outcomes. As cognitive abilities in

childhood require the diffuse recruitment of a large number of neural areas and networks<sup>64</sup>, disturbance of fetal brain development may have had a particular effect on cognitive function.

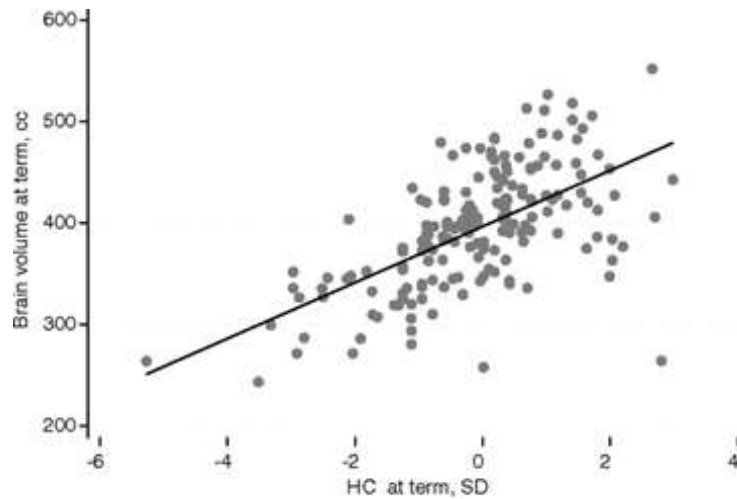


**Figure 8.4.** The associations between HC (SD) and brain volume (total intracranial volume minus CSF volume) at term (Cheong et al., 2008)<sup>3</sup>

Brain growth in the third trimester is not uniform, however, and has been shown to vary by region in both humans and animals. Imaging studies in both humans and animals have shown some nuance, however, identifying that particular neural regions develop at different periods (Figure 8.5). Region-specific growth trajectories may allow for region-specific vulnerabilities.

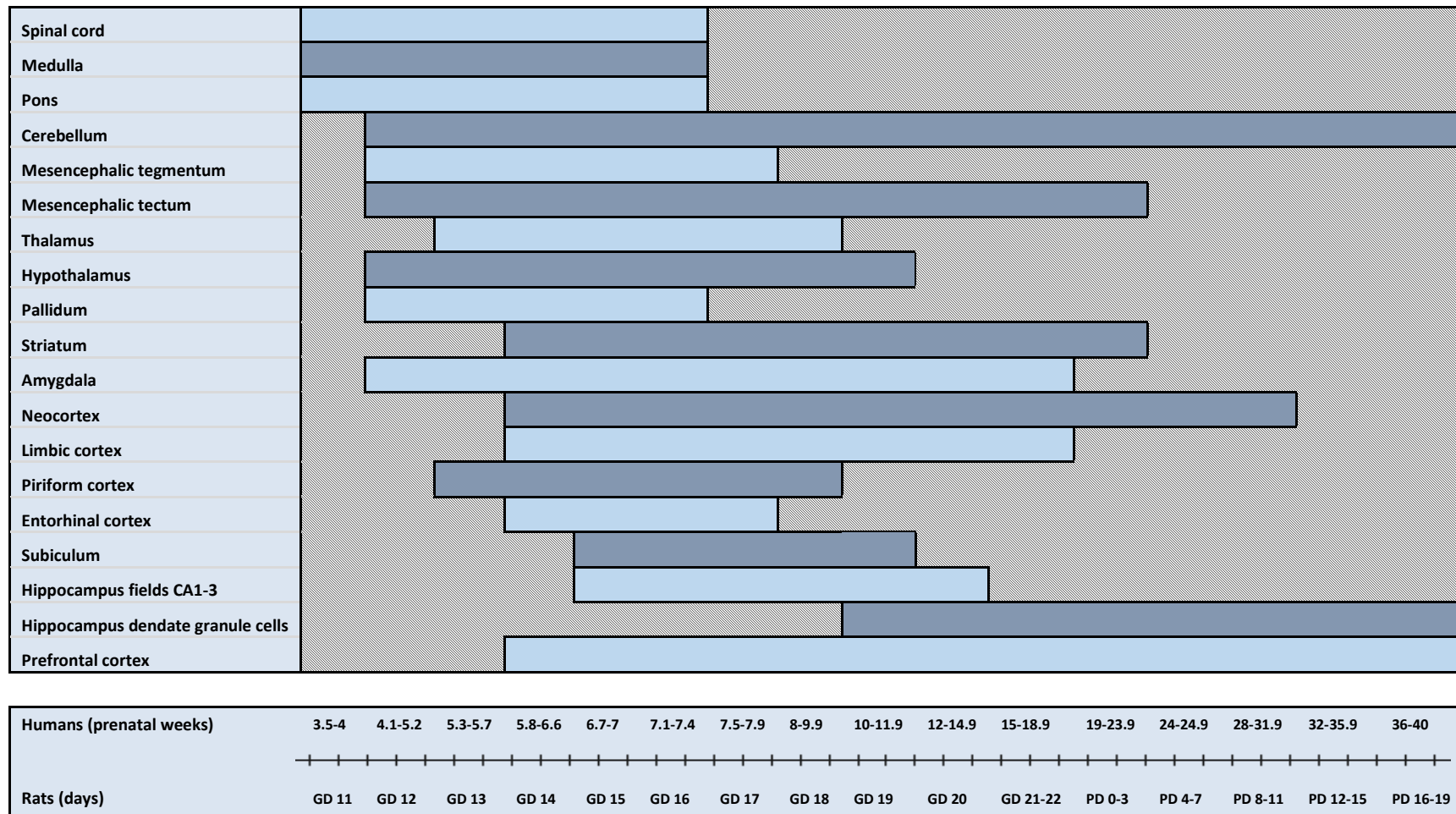


Figure 8.5. Estimated timelines of regional neurogenesis in rats and humans. Adapted from Rice and Barone (2000)<sup>41</sup>; GD = gestational days; PD = postnatal days.

One neural structure shown to play an important role in cognition is the frontal cortex. This area has been linked to a range of cognitive abilities, including working memory, preparatory set, and response inhibition<sup>65,66</sup>. Fetal growth impairment has been demonstrated to lead to a reduction in frontal volume, identifiable through both MRI<sup>59</sup> and sonographic biometric estimation<sup>67</sup>. Not only is frontal volume generally reduced in growth impaired fetuses, but it is also reduced relative to *total* intracranial volume. This suggests preferential reduction of the frontal lobe following fetal growth impairment<sup>68</sup>. Frontal lobe measures, specifically Sylvian-callosal distance, frontal triangular area, and fontanellar-callosal distance have been demonstrated to be strongly correlated with HC in infants born SGA<sup>67</sup>. This suggests that a decrease in HC during fetal development may be an indicator of frontal lobe growth restriction. Frontal growth restriction may lead to frontal-related symptoms as the infant develops, particularly executive function<sup>69</sup>, working memory<sup>70</sup>, impulse control<sup>70</sup> and learning abilities<sup>71</sup>. As such, restricted frontal-lobe development associated with late-onset fetal growth impairment may underpin the association between small HC and poorer cognitive outcomes childhood.

Another region important for cognitive abilities, which has been demonstrated to be particularly susceptible to fetal growth impairment during late gestation, is the hippocampus. The hippocampus plays a crucial role in temporal information processing, including moment-to-moment integration of spatial information processing, temporal sequencing and formulating relationships between objects and the environment<sup>72</sup>. As such, it plays a fundamental role in learning and memory<sup>65</sup>. The hippocampus has been demonstrated to be affected by an adverse prenatal environment<sup>73</sup>, and previous studies have demonstrated LBW to be associated with low hippocampal volume<sup>65</sup>. Furthermore, animal models of fetal growth impairment have demonstrated effects on hippocampal architecture, with reduced placental blood flow during the second half of gestation leading to a 30% reduction in the number of hippocampal neurons<sup>74</sup>, and retarded hippocampal arborization<sup>75-77</sup>. Morphological changes in the hippocampus may

thus be an important neurological mechanism linking impaired fetal growth to poorer cognitive outcomes in childhood.

A low PI at birth was also shown to be associated with poorer cognitive outcomes. Generally, a low PI at birth reflects either failure to gain weight or weight loss in the last trimester of pregnancy<sup>78</sup>, a period characterized by the advancing accretion of adipose tissue<sup>62</sup>. The PI has been shown to be a good correlate of total percent body fat and skin-fold thickness<sup>21,79</sup>, established biological indicators of adiposity. The association between low adiposity and poorer cognitive outcomes may lay in epigenetic changes during development<sup>80</sup>. Adipose tissue produces and secretes a number of hormones, such as leptin, a member of the adipocytokine family. Leptin has been suggested to play a key role in both fetal growth<sup>81</sup> and neural development<sup>82</sup>. In animal studies, leptin has been shown to play a crucial developmental role in neurogenesis, axon growth, and synaptogenesis, in both the hippocampus<sup>83</sup> and the cortex<sup>84</sup>. In humans, low adiposity can lead to a decrease in leptin levels<sup>85</sup>, and neurostructural abnormalities<sup>86</sup>. Reduced leptin levels in humans have also been shown to be associated with reduced cognitive abilities<sup>87,88</sup>. Furthermore, a case study of a 7-year-old leptin-deficient child showed leptin replacement lead to an improvement of anthropometric parameters and had a marked positive effect on cognitive abilities<sup>89</sup>. As such, the effects of low adiposity may result in epigenetically-mediated alterations in the development of neural regions critical for cognitive function in childhood.

Low adiposity may also have an effect on myelination. The myelin sheath is composed of approximately 70% lipids, and myelin integrity is critical for the normal function of axons in the nervous system<sup>90</sup>. Low adiposity has been linked to low levels of dietary essential fatty acids, which have also been shown to play a role in normal myelin function<sup>91,92</sup>. As such, processes that lead to reduced adiposity may also lead to delayed myelination, and thus impaired

neurodevelopment. Impairments in the myelination process and in cognitive function have been shown in postnatal iron deficient rodents and humans<sup>93</sup>.

There were no associations with PI-for-age. As adipose tissue accrues cumulatively during the final trimester of fetal development, these findings could suggest that failing to reach a general threshold of adiposity has a greater effect on cognitive development than the relative accretion of adipose tissue for GA. Given the evidence in humans above, and particularly the role of leptin replacement in improving cognitive abilities<sup>89</sup>, this is plausible. Alternatively, the associations with low PI may be residually reflective of developmental immaturity associated with shorter gestation, however given biological connection between leptin and neural development<sup>83,84</sup>, and associations with cognition<sup>87,88</sup>, it is unlikely that findings are merely residual.

### **8.5.1 Potential mechanisms underlying the effect of FCR on neurodevelopment**

The results from the current thesis provide some support for an association between FCR and poorer attention and cognitive outcomes, with some associations identified between a large HC relative to a reduced BL or BMI. Asymmetric growth restriction (as reflected by a high HC/BMI or HC/BL ratio), is suggested to result from FCR, in response to intrauterine insult (such as placental insufficiency). FCR preserves the HC at the expense of other downstream organs<sup>94-96</sup> thus reflecting a defensive adaptation response, traditionally referred to as 'brain sparing'<sup>97</sup>. The use of the term 'sparing' encapsulates the historical belief that FCR provides protection against neural insult associated with suboptimal intrauterine environment. Doppler studies however, as shown in the systematic review (Chapter 2), have now refuted this theory, suggesting that FCR may in fact indicate *increased* severity of fetal growth impairment and an increased risk for poor neurodevelopmental outcomes<sup>98</sup>. Associations between a high HC/BMI ratio and poor cognitive outcomes and a high HC/BL ratio and poor attention outcomes identified in the current thesis provide some support for this theory.

The systematic review directly examined the effects of FCR across the domains of behaviour, cognitive, language, vision and motor development. In behavioural, cognitive, language, and visual development, the presence of FCR was associated with poorer outcomes. Interestingly, however, there was no association between FCR and motor outcomes. These findings are in line with previous studies that have found negative effects of FCR on cognition, but not on motor development<sup>99,100</sup>. Recent evidence suggests that increased perfusion of the fetal brain is not uniform across the entire cerebral circulatory system, but rather varies across regions<sup>101,102</sup>. Increased cerebral blood flow has been shown to lead to the progressive deterioration of frontal-lobe growth, as blood is preferentially directed to the brain stem and basal ganglia<sup>102,103</sup>. This suggests a hierarchical order in the protection of neurodevelopmental function associated with FCR. In the presence of sustained insult, a hemodynamic shift occurs from the frontal areas, responsible for higher cognitive and behavioural functions, towards regions controlling motor functions and basic survival. This may provide an explanation for the finding of the current thesis that FCR was associated with impairment of frontal-related domains, specifically cognition and attention (Figure 8.6).



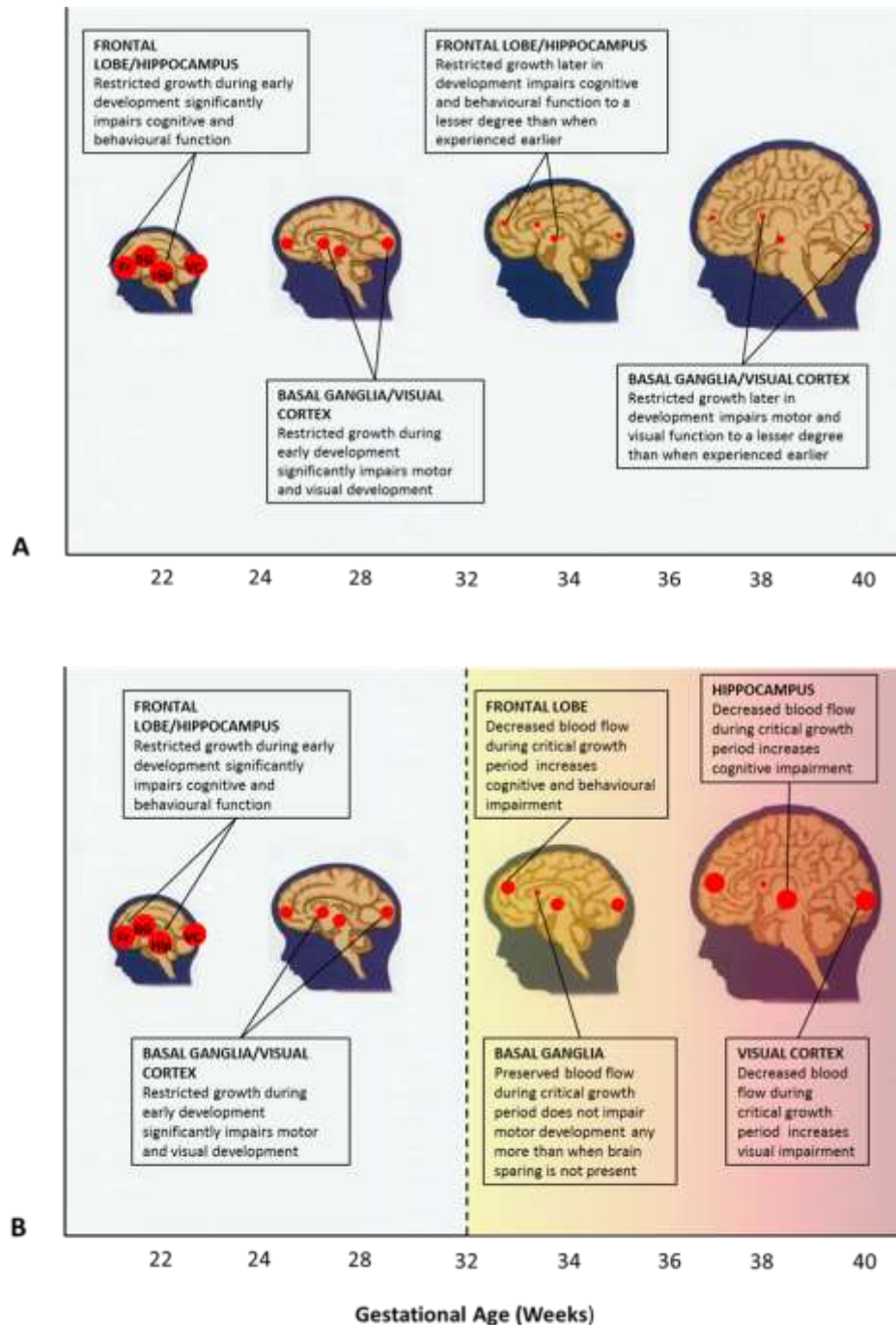


**Figure 8.6. Regional-specific neurodevelopmental effects of fetal growth impairment with and without FCR. (A) The effect of fetal growth impairment on neural development *without* FCR, and associated functional deficits. The extent of impairment is greatest when IUGR occurs early in gestation, and decreases as gestation progresses; (B) The effect of fetal growth impairment on neural development *with* FCR, occurring at 32 weeks, and associated functional deficits. In the presence of FCR, blood is directed away from neural areas such as the frontal lobe, visual cortex and hippocampus, in favour of the basal ganglia. This leads to increased impairment in visual, cognitive and behavioural function in childhood, but not in motor function; Fr=Frontal Lobe; BG=Basal Ganglia; Hip=Hippocampus; VC=Visual Cortex.**

## **8.6 Sex-specific differences in the association between fetal growth and attention development in childhood**

The analysis of sex-specific effects in the current thesis identified consistent sex differences in the associations between BL and attention outcomes. The association was shown to be much stronger in females. This pattern was evident across high-, middle- and low-income countries, suggesting that this moderation effect is not explainable by differences in underlying confounding structures and thus may have a physiological basis (discussed further in section 8.7). This finding provides some support for the hypothesis that there are stronger associations between fetal growth and neurodevelopmental in females, although this effect was only identified for attention outcomes.

This finding is in support of Eme's gender paradox<sup>104</sup>, which observed that the sex less frequently affected with a childhood disorder (i.e. girls with attention problems), are more likely to be more severely 'afflicted' (i.e. have a defective genetic and/or environmental background such as prenatal growth disturbance). Two theoretical models associated with this observation were introduced in Chapter 1, the polygenetic multiple-threshold model and the constitutional variability model. These models converge on the idea that females with neurodevelopmental difficulties are more likely to have increased defective genetic or environmental backgrounds compared to males. They diverge, however, in whether the sexes differ in their level of underlying vulnerability (the former assumes equal vulnerability but different threshold, whereas the latter assumes differential underlying vulnerability). The findings of the current thesis showed a female-specific vulnerability to the effects of fetal growth impairment on attention development in childhood, providing support for the constitutional variability model.

The constitutional variability model draws on the knowledge that male and female fetuses develop differently, and exhibit sexually dimorphic responses to the same environmental and biological risk factors. A recent review suggested that the key physiological

mechanism underpinning these sex-specific responses may be differences in the way that female and male fetuses adapt to sub-optimal intrauterine environments<sup>105</sup>. Differential adaptation strategies may lead to both differential growth trajectories and long-term outcomes, providing explanation for the female-specific association between impaired fetal growth and attention impairment.

Whereas male fetuses have been shown to adapt placental function under adverse intrauterine conditions to promote continued growth, female fetuses adapt to adverse conditions by reducing growth in an attempt to survive further environmental insults<sup>105</sup>. The continued growth of male fetuses in adverse intrauterine environments thus places them at risk of compromise in the presence of further environmental stressors, possibly accounting for the higher risk of mortality in males, but larger size at birth. Conversely, female fetuses are more 'responsive' in adverse intrauterine environments, leading to growth restriction and smaller size at birth, but promoting overall survival. Evidence for these hypotheses have been shown in both human<sup>106,107</sup> and animal studies<sup>108</sup>.

These differential adaptive mechanisms may result in a difference in long-term outcomes of fetal growth impairment for males and females<sup>109</sup>. The findings of the current thesis are in support of this, showing that the associations between fetal growth and long-term neurodevelopmental impairment are moderated by sex. These differences in fetal adaptation and the effect on attention development are illustrated in Figure 8.7.

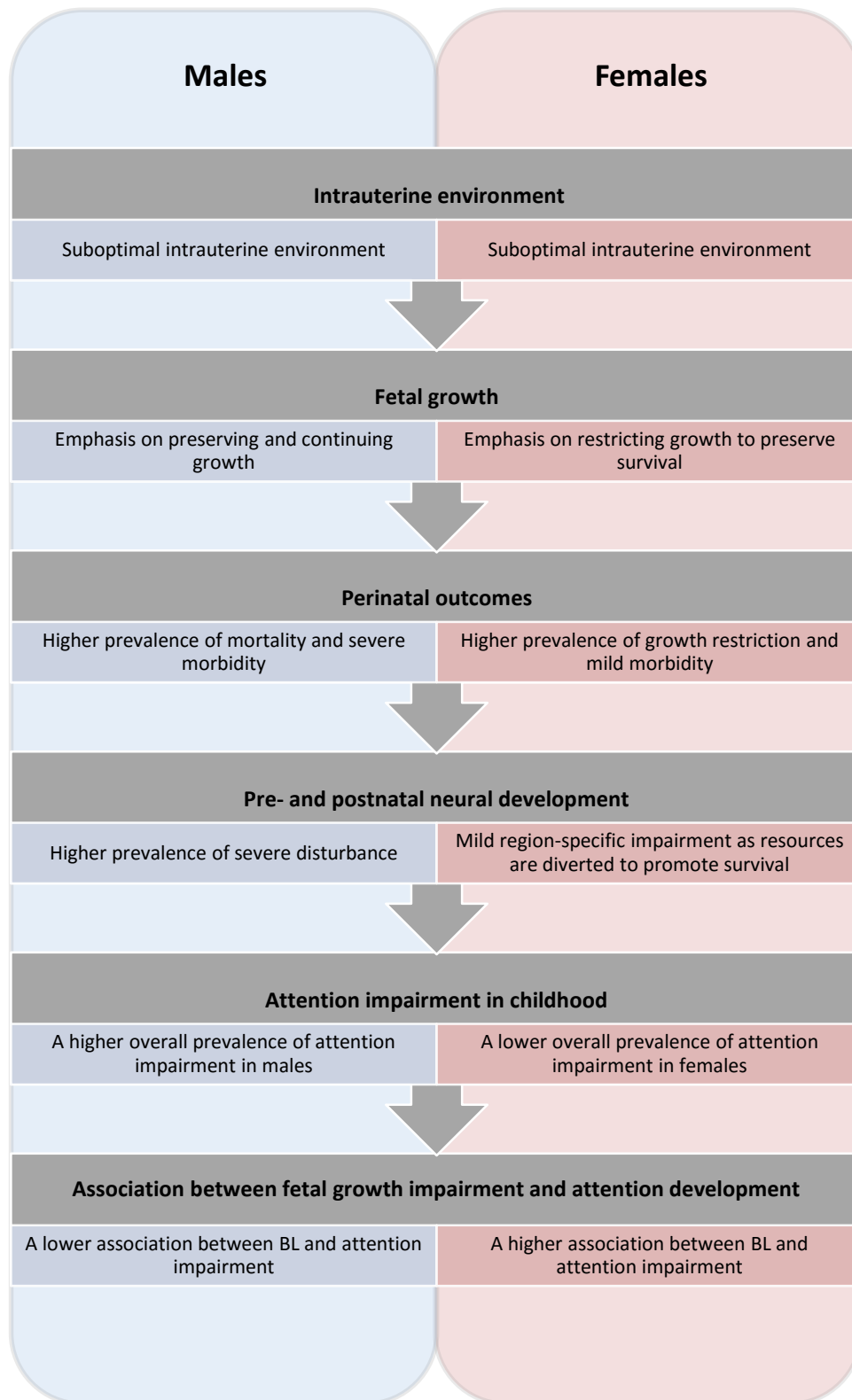


Figure 8.7. Sex differences in fetal growth and neurodevelopmental outcomes

### **8.6.1 Evidence of female-specific vulnerability to impaired fetal growth**

The idea that the etiological pathway between fetal growth and attention problems may be moderated by sex is receiving increasing attention<sup>109,110</sup>. Previous research has shown female fetuses to have a specific vulnerability to certain prenatal risk factors, supporting the female-specific vulnerability to negative outcomes associated with fetal growth impairment, identified in the current thesis. Female fetal development has been identified to be particularly vulnerable to the effects of gestational factors such as diabetes<sup>111</sup>, maternal smoking<sup>112,113</sup> and alcohol consumption<sup>114,115</sup>. Interestingly, each of these gestational risk factors is likely to be sustained throughout pregnancy (rather than transient). It is sustained risk throughout pregnancy that is also likely to lead to reduced BL<sup>11</sup>. Furthermore, each of these sustained prenatal risk factors been associated with the later development of attention problems<sup>116-118</sup>.

Studies examining the mechanisms of these sex differences have shown sex-specific effects of fetal insult on the development of neural structure and function, which may underpin specific associations with attention impairment. Female-specific effects of intrauterine insult have been linked to the development of the hypothalamus and the HPA axis, both of which play a role in attention function. For example, a female-specific vulnerability to attention impairment has been shown following intrauterine hyperglycemia<sup>111</sup>. Intrauterine hyperglycemia leads to morphological disturbances in the neural architecture of the hypothalamus<sup>119,120</sup>, which has been shown to play a role in attention function<sup>121</sup>. As such, female-specific vulnerability to the effects of intrauterine hyperglycemia on attention development may be mediated by female-specific effects on the hypothalamus.

Another female-specific effect has been identified in the association between prenatal maternal stress and attention impairment<sup>122</sup>. These effects have been suggested to be mediated through increased maternal cortisol, resulting in impaired fetal development of the HPA axis and autonomic nervous system<sup>123</sup>. These systems are important for attention regulation<sup>124</sup>. A review

by Kaiser et al. (2005)<sup>125</sup> identified that several animal studies have indicated more behavioural problems in female offspring following exposure to prenatal stress. Similarly, studies in humans have shown that maternal anxiety is associated with increased behavioural problems in girls, not boys<sup>126,127</sup>. One study examined the effects of prenatal stress on neural development at 7 years of age, and found specific effects of prenatal stress in females, but not males<sup>128</sup>.

In sum, sex-specific research suggests that female fetuses may have a specific vulnerability to certain intrauterine exposures, leading to structural and functional neural changes in utero, which then manifest as poor attention outcomes in childhood. The findings of the current thesis support this research, identifying a female-specific vulnerability to poor attention outcomes associated with impaired fetal growth.

## **8.7 Differences between high-, middle- and low-income countries**

The current thesis examined differences between high-, middle- and low-income countries by comparing three samples drawn from geographically diverse cohorts (Chapter 5), and by performing within-cohort comparison of low-risk samples across the INTERGROWTH-21<sup>st</sup> sites (Chapter 6). This is important because very few studies had been previously conducted in LMICs. It was hypothesised that stronger associations would be identified between fetal growth and neurodevelopment in LMICs (compared to HICs), where the rate of perinatal problems and neuroimpairment is higher. The hypothesis was partially supported, identifying a stronger association between birth anthropometric indices and cognitive outcomes in LMICs. No difference was identified, however, between LMICs and HICs in attention outcomes: the association between birth anthropometric indices (specifically BL) and attention outcomes were originally identified as stronger in HICs (Chapter 5), however were also revealed in LMICs when the analysis was conducted separately for females and males (Chapter 7).

Previous studies examining associations between fetal growth and neurodevelopmental outcomes, have been largely conducted in HICs including Israel, Spain, Canada, Italy, UK, The

Netherlands, Austria, Sweden, New Zealand, Switzerland, USA, Finland and Germany, and in Jamaica (an upper-middle income country). There have been few studies in low- and lower-middle income countries examining the effects of fetal growth impairment on neurodevelopment. The studies that *have* examined fetal growth in lower-income countries have relied on BW indices alone. In Kenya, one study of 120 LBW infants showed a 9.2% prevalence of neurological dysfunction at two years of age<sup>129</sup>, although there was no comparison with normally grown children. In India, the Pune Low Birth Weight Study of 201 LBW children<sup>130</sup> found poorer neurodevelopmental outcomes at six years of age compared to non-LBW children, although the IQ range of LBW children was still within the 'normal' range. Indices of LBW have also been shown to be associated with poorer developmental outcomes in longitudinal studies in Nepal<sup>131</sup> (a low-income country) and Guatemala<sup>4,132</sup> (a lower-middle income country).

Although some studies have examined the neurodevelopmental effects of being born LBW, the majority of research in LMICs has focussed on the effects of preterm birth (with studies conducted in Malawi<sup>133</sup>, Pakistan<sup>134</sup>, Ethiopia<sup>135</sup>, Bangladesh<sup>136</sup>, India<sup>137</sup>, the Philippines<sup>138</sup> and Nepal<sup>131</sup>), or the effects of stunting and wasting in childhood (with studies conducted in the Philippines<sup>139</sup>, Peru<sup>140</sup>, Guatemala<sup>141</sup> and Indonesia<sup>142</sup>). Pooled analyses of a number of these studies have concluded that preterm birth<sup>138</sup> and stunting and wasting in childhood<sup>9</sup>, affect long-term neurodevelopment. No studies had previously examined the effects of stunting, wasting or asymmetry *at birth* on childhood neurodevelopmental outcomes in LMICs. The current thesis suggests that in LMICs, low BL is associated with poorer attention outcomes, whereas restricted HC and low PI at birth are associated with poorer cognitive outcomes. Interestingly, the associations between birth anthropometric indices and poorer cognitive outcomes appeared to be stronger in LMICs than HICs.

Although the immediate sequelae of severe fetal growth impairment are similar across populations (e.g. neonatal mortality or significant disability), the longer-term consequences of

growth on neurodevelopmental outcomes may differ across populations because of interactions with influences from different confounding structures (such as nutritional factors, early childhood development, education, and medical care)<sup>11</sup>. The current thesis used conservative statistical adjustment to test the robustness of associations against potential confounding, however residual confounding may still be likely<sup>143,144</sup>. This may be due to a) the inability to measure and control for all possible confounding variables and b) the inevitable imprecise measurement of confounding variables<sup>143</sup>.

Comparing associations between HIC and LMIC cohorts allows testing of the associations in the presence of different confounding structures. Confounding structures include any factors which may have an effect on the association, such as health, socioeconomic and demographic factors. This technique has been established in epidemiology as a method to improve causal inference<sup>145,146</sup>. It has been previously used to provide evidence for causal associations between pre- and postnatal factors, including maternal smoking<sup>146</sup> and breastfeeding<sup>145</sup>, and childhood outcomes. According to this method, similar associations across cohorts with different confounding structures (i.e. HIC and LMIC cohorts) suggests some causal inference in an association, as the association is robust to heterogeneous confounding effects. This provides support for biological mechanisms underpinning associations.

Conversely, differences in associations across cohorts with different confounding structures suggest that influences from confounding structures may play an important role. For example, if the association between fetal growth and child neurodevelopment is due to confounding by socioeconomic and healthcare factors, then the associations would be expected to differ between cohorts where these confounding structures are different.

The current study identified associations between BL and attention outcomes in cohorts from high-, middle- and low-income countries, suggesting that there may be a direct physiological link between impaired fetal growth and attention development, which is relatively



robust to the effects of different confounding structures. For cognitive outcomes, however, the associations were identified to be much stronger in LMICs compared to HICs, suggesting that confounding structures in LMICs may play a role in moderating the association between impaired fetal growth and cognitive outcomes.

One way in which the effects of confounding structures may differ between HICs and LMICs may be in the way they affect fetal growth. It has been shown that the factors which impact fetal growth within populations are not necessarily the same as those which operate between populations<sup>147</sup>. A study examining the factors contributing to global variation in stunting and wasting<sup>148</sup> showed that most between-country variation for stunting and wasting was explained by: food security, maternal and child care, health services and environment, institutions and potential resources, explaining 76% of the national variation in stunting and 66% of the national variation in wasting. Between-country stunting variation was mostly explained by energy availability, female literacy and gross national product. The association between stunting and health expenditure differed by region, with strongest associations in Africa and Asia. Wasting mostly varied between countries as a function of national immunization rate (lower immunisation was associated with higher wasting), and for Asia only, energy availability.

The association between stunting and wasting and neurodevelopmental impairment in LMICs has been commonly attributed to fetal (secondary to maternal) malnutrition. A recent Lancet series showed a significant loss of developmental potential in LMICs associated with the effects of maternal and child malnutrition on growth<sup>149</sup> and growth on neurodevelopmental impairment<sup>50</sup>. The association between stunting and neurodevelopment in LMICs was hypothesised to be largely to nutritional deficits arising from poverty (Figure 8.8).

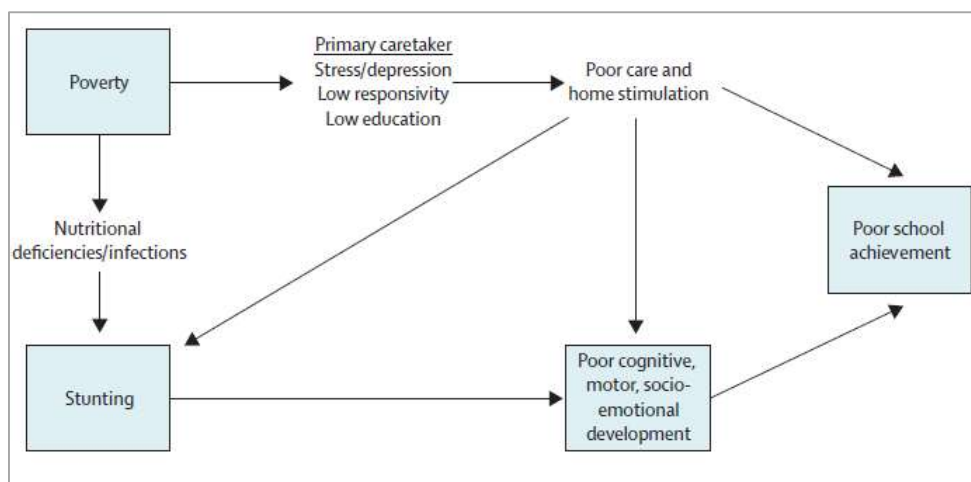


**Figure 8.8. Hypothesised association between poverty, stunting, child neurodevelopment and school achievement in LMICs<sup>50</sup>**

Given that mothers from LMICs in the INTERGROWTH-21<sup>st</sup> study were not malnourished, but associations between growth and cognitive outcomes were still more evident than in HICs, the stronger associations in LMICs in the INTERGROWTH-21<sup>st</sup> cohort are likely due to differences in confounding structures other than nutrition. This suggestion was supported by the finding in Chapter 6 Study II, which showed that although having a low-risk mother may provide some protection against the negative outcomes associated with impaired fetal growth, there are still some residual associations identifiable.

One difference identified in the INTERGROWTH-21<sup>st</sup> cohort in potential confounding structures between HICs and LMICs, was the prevalence of caesarean delivery. Brazil, India and Kenya all had a higher prevalence of caesarean delivery than the UK and Italy. Interestingly, there was also a clear pattern in how these rates compared to the respective national averages, with rates in Brazil, India and Kenya all significantly higher than national averages, and the UK and Italy below national averages (Table 8.2).

**Table 8.2. Differences between national average and INTERGROWTH-21st caesarean rate by site**

| Country       | National average <sup>150</sup> | INTERGROWTH-21 <sup>st</sup> | Difference <sup>i</sup> | Below/above <sup>ii</sup> |
|---------------|---------------------------------|------------------------------|-------------------------|---------------------------|
| <b>UK</b>     | 22.0%                           | 16.1%                        | -5.9%                   | Below                     |
| <b>Italy</b>  | 38.2%                           | 22.3%                        | -15.9%                  | Below                     |
| <b>Brazil</b> | 45.9%                           | 85.8%                        | +39.9%                  | Above                     |
| <b>India</b>  | 8.5%                            | 55.2%                        | +46.7%                  | Above                     |
| <b>Kenya</b>  | 4.0%                            | 33.9%                        | +29.9%                  | Above                     |

<sup>i</sup> INTERGROWTH-21<sup>st</sup> minus national rate; <sup>ii</sup> Compared to national rate

This pattern possibly reflects observations of stronger social patterning of caesarean sections in LMICs compared to HICs<sup>151</sup>. Overall, strong socioeconomic differentials in the rates of caesarean delivery have been identified in LMICs<sup>151</sup> (Figure 8.9), patterns that are not evident in HICs. In Brazil, caesarean delivery is associated with higher maternal education, higher income and urban dwelling<sup>152,153</sup>. Similarly, in both India and Kenya, caesarean delivery is associated with higher income and urban dwelling, with the highest rates among the ‘urban rich’ and lowest among the ‘rural poor’<sup>154</sup>. These socioeconomic differentials associated with caesarean delivery are not evident in HICs, as has been shown in both the UK<sup>155</sup>, and Italy<sup>156</sup>.

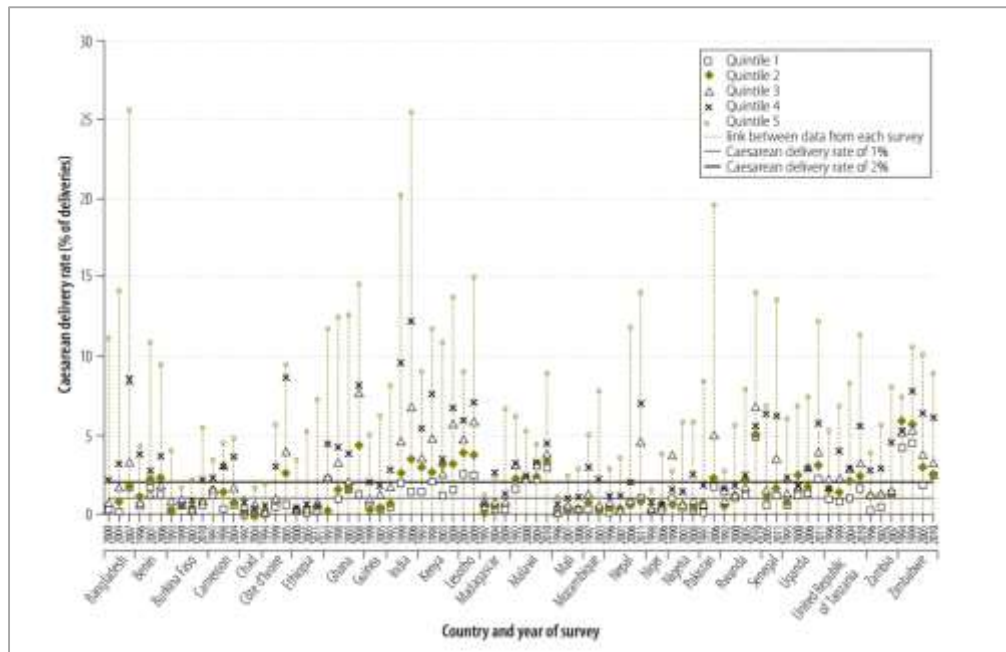


**Figure 8.9. Caesarean delivery rates by country, survey year and wealth quintile in southern Asia and sub-Saharan Africa (1990-2011)<sup>154</sup>**

A higher rate of caesarean delivery increases the risk of morbidity for both mother and child<sup>157-159</sup>. Furthermore, specific associations have been shown between caesarean section and fetal growth impairment<sup>160</sup> (as fetal growth impairment is an indication for caesarean delivery<sup>161</sup>). As such, higher rates of caesarean delivery, reflects the social patterning in LMICs, and could be a possible confounding structure augmenting the association between fetal growth and cognitive outcomes in LMICs.

In summary, there are many confounding structures that may enhance the association between fetal growth impairment and poor cognitive outcomes in LMICs. Although some of these are not relevant to a low-risk sample (such as maternal malnutrition), there may be other factors in LMIC low-risk samples, such as high caesarean delivery rates, contributing to stronger association between fetal growth impairment and poor cognitive outcomes. These differences

in associations and underlying structures highlight the pressing need for specific research into the effects of impaired fetal growth in LMICs.

## **8.8 Methodological strengths and limitations**

### **8.8.1 Original contributions**

The research in the current thesis has a number of original contributions. To the author's knowledge, this is the first study to directly compare the effects of a wide range of fetal growth phenotypes (BW, stunting, wasting and asymmetry) on attention and cognitive outcomes in childhood.

Secondly, there have been very few studies previously conducted in LMICs. Much of the current knowledge of the effects of growth on neurodevelopment has been extrapolated from populations in HICs, which have a lower rate of fetal growth impairment<sup>162</sup> and neurodevelopmental disorders<sup>163</sup> and where confounding structures differ<sup>164</sup>. The current thesis included populations from an upper-middle income country (Brazil), a lower-middle income country (India), and a low-income country (Kenya), for comparison with populations from HICs (UK and Italy). Furthermore, the methodology employed was consistent across sites of the INTERGROWTH-21<sup>st</sup> cohort, which allowed direct cross-site comparison. The results showed differences between LMICs and HICs in both association strength and confounding structures, suggesting that findings in HICs are of limited validity in LMIC populations, and greater emphasis is needed on research in LMICs.

A third contribution is the examination of sex differences in the association between fetal growth and attention and cognitive outcomes. Despite clear and established sex differences in neural development, fetal growth, and neurodevelopmental disorders, there is a paucity of research into sex differences in the association between fetal growth and neurodevelopmental outcomes. The current findings provided support in three separate cohorts for a female-specific effect of fetal growth impairment on attention development.

A final contribution of this research was the validation of the INTER-NDA, as a screening tool for neurodevelopment in infants aged 22-28 months. Currently, there is no validated screening tool which is quick and easy to administer, by non-specialists, in low-resource settings. The validation of the INTER-NDA makes available a scalable solution to the challenge of early detection of neurodevelopmental impairments by providing a rapid, easy to administer screening tool for widespread use in community-based practice.

### **8.8.2 Strengths of methodology**

The research methodology in the current thesis has a number of strengths. Firstly, the research questions were data-driven, drawing on the findings of the systematic review (Chapter 2) to determine the scope of the current thesis. It revealed a number of research questions that remained unanswered, such as the paucity of research comparing different fetal growth phenotypes, the paucity of research in LMICs, and the conflicting results on potential sex differences. This was used to guide the development of the research questions of the remainder of the thesis.

A methodological strength of the current thesis is in the use of multiple longitudinal, prospective cohorts to test associations. Prospective birth cohort studies follow a large number of children, and thus have good power to determine associations which may be otherwise missed. Furthermore, they have a large amount of data on potential confounding factors for statistical adjustment. Not only were three cohorts compared, but they were specifically chosen to be drawn from different geographical locations, and from countries with different national income-levels. This has the dual benefit of a) allowing inference to be made beyond the population from which the sample is drawn, and b) revealing information about the effects that different confounding structures may have on the associations.

The INTERGROWTH-21<sup>st</sup> Project is unique in that the same standardised protocol for all assessments was implemented across all sites. There was uniform methodology for

anthropometric assessments, and uniform protocol for the estimation of GA. The neurodevelopmental assessment at 2 years was also carried out in accordance with a standardised protocol, with identical training, monitoring and quality assessment across sites.

The Pelotas and ALSPAC cohorts have strong external validity to the population from which they were drawn, as they enrolled *all* consenting mothers within a temporal and geographical period, without restriction (included both high- and low-risk mothers). As such, these cohorts are likely to be representative of the population from which they were drawn (although the possibility must be considered that increased and continued contact with health care workers and researchers may modify outcomes).

When comparing across cohorts however, it is important to limit diversity (as much as possible for established cohorts) that may be introduced through different exposure and outcome variables. A strength of the current thesis was that it addressed this in a number of ways. Firstly, birth anthropometric indices were limited to those that were available for all three cohorts. Tenth percentile cut-off points were chosen for consistency with previous research and global recommendations on birth anthropometric indices provided by the WHO<sup>11</sup>. For each of the birth anthropometric indices, various references were used (e.g. MGRS *and* INTERGROWTH-21<sup>st</sup>), which a) reduced over-reliance on any one specific growth reference/standard (as all have inherent strengths and limitations), and b) allowed direct comparison of predictive abilities of the different references/standards.

### **8.8.3 Limitations of methodology**

There are some limitations to the current research which must be considered when interpreting results. These are grouped as a) those arising from the use of prospective birth cohorts (such as error variation and heterogeneity of neurodevelopmental measures), b) those related to the use of anthropometry at birth as an indicator of fetal growth, and c) statistical considerations.

Firstly, there are inherent restrictions associated with using data collected from prospective birth cohort studies, regarding the selection of exposure, outcome and confounding variables, and the error associated with different measurement protocols. The use of established cohorts means that there is limited ability to tailor the research (such as measures used, assessment protocol, or age at follow-up) to the specific question being asked. As such, research questions and scope must be clearly decided upon *a priori*, with strong theoretical justification. A summary and rationale of the scope of the research design and methodology is provided in section 3.7. There was also some data not available for use in the current thesis across the three cohorts (such as ethnicity data for the INTERGROWTH-21<sup>st</sup> cohort) which may have been useful in explaining observed associations. Furthermore, there is variability across the three cohorts regarding rates of attrition. Despite this, however, attrition analyses presented in Chapter 5 showed no unexpected differences between the final sample and those lost-to-follow-up (Table S5.1).

The use of established cohorts means that there is an inability to control variation in error measurement across the three cohorts, which may be introduced as a result of systematic protocol differences. Such differences in measurement error may have been introduced in anthropometric measurements, estimations of GA and follow-up assessments. For anthropometric measurements, there were differences between the measurement protocols surrounding the number of measurements taken, the training and professional background of the anthropometrists, and the source of the data. For example, measurements of BW were collected by maternity staff in the Pelotas birth cohort, from birth records in the ALSPAC cohort, and by two trained researchers in the INTERGROWTH-21<sup>st</sup> cohort. As the primary aim of INTERGROWTH-21<sup>st</sup> is to create standardised growth charts, anthropometric measurements have been strictly controlled and monitored, and conducted by highly trained assessors<sup>165</sup>. This same level of control was not built into the study design of the Pelotas or ALSPAC assessments (as anthropometry was not the overarching interest), which must be acknowledged when



interpreting results. Similarly, there is also increased error in the assessment of GA in the ALSPAC and Pelotas cohorts, compared to the INTERGROWTH-21<sup>st</sup> cohort. This is important as the INTERGROWTH-21<sup>st</sup> standards require knowledge of GA age at birth to identify growth restricted neonates<sup>166</sup>.

There may also be systematic differences in the error associated with follow-up assessments, which used different assessment tools at different ages. Attention assessments were conducted using the CBCL 1.5-5<sup>167</sup> at 2 years in INTERGROWTH-21<sup>st</sup>, the CBCL 4-18<sup>168</sup> at 4 years in Pelotas, and the SDQ<sup>169</sup> at 6 years in ALSPAC. Cognitive development was assessed using the INTER-NDA<sup>170</sup> at 2 years in INTERGROWTH-21<sup>st</sup>, and the WPPSI-R<sup>171</sup> at 4 years in Pelotas and ALSPAC. These assessments have different sensitivity to identifying attention and cognitive impairment. The sensitivity of the CBCL 1.5-5 for identifying children who have been clinically referred for developmental assessment has been shown to be 27.0%<sup>167</sup>, and sensitivity for the CBCL 4-18 has been shown to be 68.8%<sup>172</sup>. The sensitivity of the SDQ (taken from a sample of 5-10 year olds) has been shown to be 75.2%<sup>173</sup>. For the cognitive assessments, the sensitivity of the INTER-NDA to detect children with clinically-diagnosed impairments or school achievement has not yet been assessed, although Chapter 4 (Table 4.10), showed the sensitivity of the INTER-NDA to identify children with an extremely low BSID-III score (<2SD) was 100%. This, however, may be inflated by the fact that the INTER-NDA is largely comprised of a subset of the BSID-III, and that the assessments on the INTER-NDA were conducted from video recordings of the children completing the BSID-III. The association between the scores of the INTER-NDA and the BSID-III was strong ( $r=0.83$ ). For the WPPSI-R, the association of the WPPSI-R FSIQ score with school achievement at 5.5 years has been shown to be moderate ( $r=0.60$  for maths, and  $r=0.45$  for literacy)<sup>174</sup>.

Attention assessments were conducted by parental-report measures, which require subjective assessment of child behaviour. This parental-report measures the behavioural

manifestation of attention problems in childhood, related to the ‘endogenous’ attention system in children. Endogenous attention includes constructs of attention span, distractibility and persistence (covered further in the general introduction, Chapter 1). There was some variation identified in the prevalence of attention impairments across sites, for example attention impairments were identified as much higher in India compared to other INTERGROWTH-21<sup>st</sup> sites. It is possible that these reflect true variation in the prevalence of impairments, however it also must be acknowledged that underlying cultural differences in parental perception of problem behaviours, and the threshold for reporting them, may account for the difference in observed rates of attention impairment<sup>175</sup>. Studies comparing cross-cultural parent ratings of children’s behaviour on the CBCL, however, do not suggest this<sup>176,177</sup>. Cross-cultural comparisons of item and scales scores of the CBCL in large general population samples have been published for at least 10 combinations of HIC and LMIC countries, including United States, Brazil, Kenya, Thailand, the Netherlands, China, France, Jamaica, Australia, and Belgium<sup>174</sup>. The vast majority of these studies showed cross-cultural consistency in assessments of behavioural problems<sup>177</sup>, suggesting that variation in prevalence rates may not be due to differences in parental perception or reporting of behavioural impairments.

Differences in error associated with the cognitive assessments may arise from systematic variation in administration and scoring. Even when using identical measures with standardized administration protocols (such as the WPPSI-R), it is possible that there are systematic differences in administration between cohorts, which may skew the results. Within-cohort standardized scores (Z-scores) were used to limit any systematic cross-cohort differences in administration, however possible cross-cohort administration differences must still be considered when interpreting results. There is also more error associated with the scoring the WPPSI-R, compared to the INTER-NDA, as potential scoring error in the INTER-NDA was addressed in the design of the tablet-based scoring application<sup>178</sup>. The WPPSI-R scoring system relies on hand-scored record forms and manual calculation of scaled and composite scores. It is

estimated that scoring errors occur in approximately 38.5% of assessments, accounting for inaccuracies in more than 10% of reported composite scores<sup>179</sup>.

There are also limitations which must be acknowledged when using birth anthropometric indices to draw inferences about the fetal growth process. Although birth anthropometric indices provide information about the average velocity of growth across fetal development<sup>11</sup>, they are single-point measurements, and as such, do not provide fine-grained information about the manner in which growth velocity may have differed across gestation. Furthermore, using a predefined cut-off may also lead to some misclassification of growth impaired neonates. Estimates have suggested that up to 20% of neonates classified as SGA are in fact normally grown<sup>180</sup>, and 17% of neonates classified as AGA may have been subject to fetal growth impairment<sup>181</sup>. Differences in sample size (and thus power) across the three cohorts, may mean that the INTERGROWTH-21<sup>st</sup> cohort may be more vulnerable to such effects than the Pelotas or ALSPAC cohorts.

Finally, there are some limitations surrounding the analyses which must be considered when interpreting results. Firstly, the between-site INTERGROWTH-21<sup>st</sup> analysis had some limitation arising from the reduction of power associated with splitting the cohort into site populations. Reduced power increases the likelihood of Type II error, and as such the analysis in this chapter supplemented findings of statistical significance with an examination of the pattern of ORs. As these, however, were based on largely non-significant results ( $p > .05$ ), findings of site differences are tentative, and should be interpreted as providing evidence for the requirement of further standardised research to compare populations from low-, middle-, and high-income countries. Furthermore, although all mothers were recruited to the INTERGROWTH-21<sup>st</sup> Project according to the inclusion criteria that they should be 'free from economic constraint', the proportion of mothers that meet this criteria is likely to be higher in HICs (such as Italy, for example) compared to LMICs (such as Kenya, for example). This means

that the mothers included from the lower-income samples in the INTERGROWTH-21<sup>st</sup> cohort are likely to be relatively higher-income, compared to the population from which they are drawn, than the mothers included from the Italian sample. This systematic variation in representativeness across the INTERGROWTH-21<sup>st</sup> cohort may inflate error when conducting direct between-site comparison.

A second statistical limitation surrounds adjustment for confounding, with the suggestion that adjusting for confounding variables that may be in the causal pathway (i.e. factors occurring in the intervening period between birth and follow-up) may lead to ‘over-adjustment’ of the final model<sup>182</sup>. This may lead to an inflated Type II error rate. To reduce excessive over-adjustment, it was *a priori* decided to omit postnatal growth variables as potential ‘confounders’ (e.g. intermediate size, concurrent size or growth velocity in childhood), as these are believed to be directly in the causal pathway<sup>183,184</sup>, and are of limited relevance to the theoretical framework of predicting neurodevelopmental impairment from birth.

Finally, whilst cross-cohort comparison improves causal inference, it is important to note that this approach only separates causal effects from confounding structures which differ between cohorts. Therefore, it remains possible that the consistent associations found between fetal growth variables and attentional problems across cohorts are explained by confounding variables which are also consistent across cohorts (e.g. genetic and epigenetic confounding)<sup>185</sup>. Further analysis and comparison of the strengths and limitations of each particular cohort is presented in Table 8.3.

**Table 8.3. Comparison of the Pelotas, ALSPAC and INTERGROWTH-21st cohorts on sample power, cohort strengths and weaknesses**

|                    | Pelotas 2004                                                                                                                                                                                                                                                                                                                                             | ALSPAC                                                                                                                                                                                                                                                                                                                                                                                                                             | INTERGROWTH-21st                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Power <sup>i</sup> | 0.99-1.00                                                                                                                                                                                                                                                                                                                                                | 1.00                                                                                                                                                                                                                                                                                                                                                                                                                               | 0.77-0.96                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Cohort strengths   | <ul style="list-style-type: none"> <li>• Low loss-to-follow up</li> <li>• Large amount of information on potential confounding factors</li> <li>• Externally valid for population from which sample is drawn</li> <li>• Large number of follow-up assessment times and measures</li> </ul>                                                               | <ul style="list-style-type: none"> <li>• Large sample</li> <li>• Large amount of information on potential confounding factors</li> <li>• Externally valid for population from which sample is drawn</li> <li>• Large number of follow-up assessment times and measures</li> </ul>                                                                                                                                                  | <ul style="list-style-type: none"> <li>• Geographically and culturally diverse sample</li> <li>• Sample specifically selected for mothers at low risk of growth restriction</li> <li>• Strict quality control of anthropometric assessments</li> <li>• Reduced administration and scoring error in follow-up assessment</li> <li>• Investigator had opportunity for primary data collection</li> <li>• Investigator had input into follow-up assessment</li> </ul> |
| Cohort limitations | <ul style="list-style-type: none"> <li>• Reliance on maternity staff for birth weight measurement</li> <li>• Reliance on clinically-determined gestational age</li> <li>• WPPSI-R shown to have risk of administration and scoring error</li> <li>• Restricted to choice of follow-up assessment times and measures (secondary data analysis)</li> </ul> | <ul style="list-style-type: none"> <li>• Reliance on birth records for birth weight data</li> <li>• Reliance on clinically-determined gestational age</li> <li>• Home completion of attention assessment (not in presence of researcher)</li> <li>• WPPSI-R shown to have risk of administration and scoring error</li> <li>• Restricted to choice of follow-up assessment times and measures (secondary data analysis)</li> </ul> | <ul style="list-style-type: none"> <li>• Relatively small sample size (limits power)</li> <li>• Use of (previously) non-validated neurodevelopmental assessment</li> <li>• Limited information available on potential confounding factors</li> <li>• Limited external validity for population from which sample is drawn</li> </ul>                                                                                                                                |

<sup>i</sup> Estimate based on odds ratio (OR) range = 1.20-1.30

## **8.9 Implications of findings for policy, clinical practice and research**

There are a number of important implications for the current research, traversing a number of areas including policy, clinical practice, research practice and future research directions. These are summarised in Table 8.4.

**Table 8.4. Implications of findings of thesis**

|    | Area                 | Sub-area                       | Explanation                                                                                                                                                                                           |
|----|----------------------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1  | Policy               | Educational outcomes           | Childhood attention and cognitive impairment are associated with lower academic achievement and attainment                                                                                            |
| 2  | Policy               | Health and social outcomes     | Childhood attention and cognitive impairment are associated with increased risk of psychopathology and higher incarceration rates                                                                     |
| 3  | Policy               | Economic outcomes              | Childhood attention and cognitive impairment are associated with lower earnings and higher unemployment rate                                                                                          |
| 4  | Policy               | Governmental investment        | Strong health, social and economic argument for governmental investment in reducing childhood neurodevelopmental impairment                                                                           |
| 5  | Clinical             | Neonatal measurements          | Proposed shift to routine neonatal measurements of more specific growth phenotypes (including BL and HC), to allow better identification of children at risk                                          |
| 6  | Clinical             | Increased understanding        | Increased clinical understanding of the neurodevelopmental risks associated with different phenotypes of fetal growth impairment                                                                      |
| 7  | Clinical             | Neurodevelopmental screening   | The INTER-NDA can be used as a validated neurodevelopmental screening tool, either as a global neurodevelopmental screen at 2 years, or a targeted screen for children identified as at risk at birth |
| 8  | Clinical             | Early intervention programmes  | Specific targeting of early intervention programmes (for children identified as at risk) can help children reach their neurodevelopmental potential                                                   |
| 9  | Research (practice)  | Neurodevelopmental assessments | Neurodevelopmental assessments should be disaggregated across domain, rather than as one global outcome                                                                                               |
| 10 | Research (practice)  | Sex-specific analyses          | Based on sex differences, effects of fetal exposures on childhood outcomes should be separated by sex                                                                                                 |
| 11 | Research (direction) | Fetal growth trajectories      | Future research should examine whether specific periods of fetal development may be particularly vulnerable to effects of impaired growth                                                             |
| 12 | Research (direction) | More LMIC research             | Future research needs a stronger focus on research specifically in LMICs, rather than extrapolating from HICs                                                                                         |

### 8.9.1 Policy implications

The current research showed that impaired fetal growth is associated with poorer attention and cognitive outcomes in childhood. The long-term effects of such outcomes provide social and economic arguments for governmental investment in ensuring children attain their developmental potential in both HICs and LMICs.

Sub-optimal neurodevelopment in childhood has been shown to have significant effects on educational, social and economic outcomes, increasing the demand on public health, educational and social services (e.g. through higher rates of unemployment)<sup>186-188</sup>. Furthermore, a shift to the left in the population IQ by 5 points results in a doubling of the number of individuals with IQs less than 70, which places increased demand on educational resources and social support<sup>41</sup>. Concomitantly there would also be a decrease in individuals with IQs greater than 130 by a factor of 2.5. These effects lead to an overall decrease in productivity, which has widespread societal impacts. The largest impact has been shown to be on lost earning as a result of decreased cognitive ability in childhood, which has been estimated at US\$8.15 billion<sup>41</sup>. The total cost, including increased health care, compensatory education and neonatal mortality and morbidity of offspring is estimated at \$US11.18 billion<sup>41</sup>.

The scale of impact is likely to be even higher in LMICs, with higher rates of childhood neurodevelopmental impairments. Loss of developmental potential in LMICs has been shown to lead to widespread low educational attainment, reduced earning capacity, and intergenerational transfer of disadvantage (Table 8.5), all restricting capacity for national development<sup>50</sup>. As the cost of intervention may increase and efficacy decrease with advancing age, identification at birth of future risk of neurodevelopmental impairment can significantly enhance the success and cost-effectiveness of intervention programmes.



**Table 8.5. Deficit associated with stunting, poverty (first vs third quintile of wealth), and both stunting and poverty, in schooling and percentage loss in yearly income in developing countries<sup>50</sup>**

|                  | Deficit in school grades attained | Deficit in learning ability per grade in grade equivalents | Total deficit in grade equivalents | % loss of adult yearly income per grade <sup>a</sup> | Total % loss of adult income | Number (%) of children younger than 5 in developing countries | Average % loss of adult yearly income per disadvantaged child |
|------------------|-----------------------------------|------------------------------------------------------------|------------------------------------|------------------------------------------------------|------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Stunted only     | 0.91                              | 2.0                                                        | 2.91                               | 8.3%                                                 | 22.2%                        | 92.9 (16.6%)                                                  | 19.8%                                                         |
| Poor only        | 0.71                              | ≥0.0 <sup>b</sup>                                          | 0.71 <sup>b</sup>                  | 8.3%                                                 | 5.9%                         | 62.8 (11.2%)                                                  | -                                                             |
| Stunted and poor | 2.15                              | ≥2.0 <sup>b</sup>                                          | 4.15 <sup>b</sup>                  | 8.3%                                                 | 30.1%                        | 62.8 (11.2%)                                                  | -                                                             |

<sup>a</sup> An increase of one grade of schooling is assumed to increase income by 9%. Implies that a reduction of 1 year of schooling will reduce income by 8.3% ( $1/1.09 - 1 = 0.083$ ); <sup>b</sup> Indicates that the figure is lower bound and under-estimates true figure because the effect of poverty on learning per year of schooling is unknown.

### 8.9.2 Clinical practice implications

The current thesis showed growth phenotype indicators at birth (i.e. measures of stunting and wasting) are better for predicting neurodevelopmental impairment than BW. BW indices may ‘miss’ some fetal growth impairment, as, for example, greater skeletal growth can compensate for reduced adiposity in attaining a BW in the normal range. Misclassified ‘normally grown’ neonates (based on BW) are not afforded the specialised health care that may be required<sup>189</sup>, including close neonatal surveillance, specialised postnatal care<sup>190</sup> and long-term neurodevelopmental follow-up<sup>191,192</sup>. As such, routine clinical practice should move away from using BW as a retrospective classification of fetal growth impairment to more nuanced measures of BL, HC and PI at birth. Using this information, clinicians can better identify growth impairment, and predict which children may be more at risk of neurodevelopmental impairments for targeted screening and intervention.

Early identification of children at risk is fundamental for the development and targeting of early intervention programmes. Intervention programmes are often resource-intense and as such, cannot be ubiquitously rolled-out in resource-limited settings. The INTER-NDA, validated in Chapter 4, provides a quick and easy screening tool for neurodevelopmental impairment which can help identify children for further in-depth assessment, leading to potential early intervention.

Effective interventions during early childhood may ensure children reach their neurodevelopmental potential, thus reducing academic failure and behavioural difficulties at the onset of formal schooling<sup>193,194</sup>. Current evidence-based interventions to augment neurocognitive function in early childhood in HICs include programmes such as Enhancing Neurocognitive Growth with the Aid of Games and Exercise (ENGAGE) for 3- to 4-year olds<sup>195</sup>, and Training Executive, Attention and Motor Skills (TEAMS) for 4- to 5-year olds<sup>196</sup>. There have also been a number of effective intervention programmes introduced in LMICs including

parenting support, enhanced preschool enrolment and combination interventions such as conditional cash-transfer programmes, which have been shown to improve developmental outcomes in childhood<sup>197</sup>. Furthermore, the results of this thesis suggest that there may be a level of protection for poor neurodevelopmental outcomes for children with fetal growth impairment who have low-risk mothers. Therefore, investing in programmes aimed at reducing maternal risk may be a useful way of reducing poor neurodevelopmental outcomes in children.

Taken together, the findings from this research help to enhance risk assessment at birth and screening in infancy to improve the targeting of early interventions, thus reducing childhood neurodevelopmental impairment. A possible flow chart for clinical practice is presented in Figure 8.10.

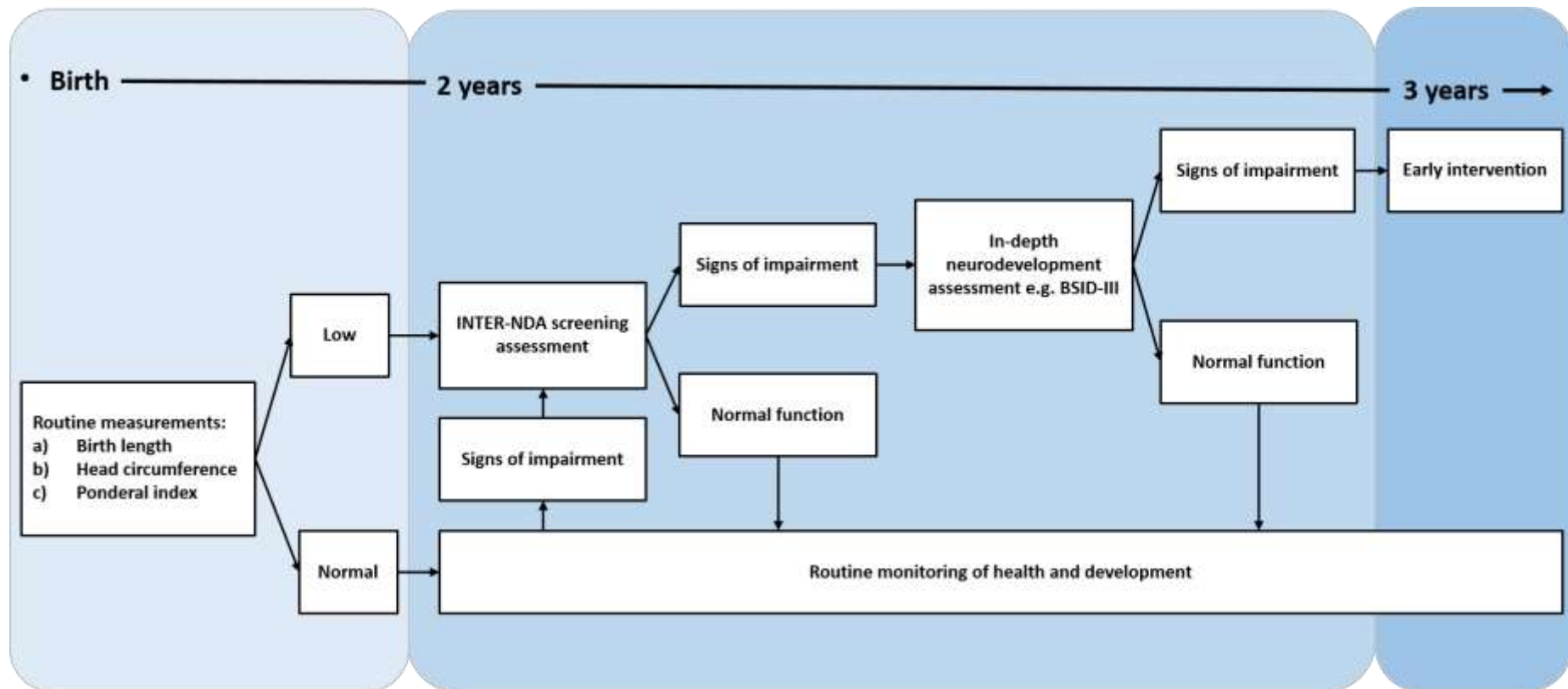


Figure 8.10. Possible flow chart for clinical practice using birth anthropometric indices and neurodevelopmental screening at 2 years of age to target early interventions

### **8.9.3 Research implications**

There are a number of research implications of the current findings, both for research practice and future directions.

#### **8.9.3.1 Research practice implications**

Firstly, the complex nature of fetal growth (specifically the variation in growth phenotype) has been shown to lead to heterogeneous neurodevelopmental outcomes. As such, research on neurodevelopmental impairment should move away from universal classifications of neurodevelopmental abilities (e.g. a 'global' neurodevelopmental outcome), and instead use domain-disaggregated designs to attain a more fine-grained examination of neurodevelopmental profiles.

Secondly, despite a large amount of research identifying sex differences in fetal growth and neural development, and childhood neurodevelopmental disorders, the vast majority of research in this field has continued to combine males and females into a homogenous group. This potentially masks sex-specific associations, and contributes to large variation in findings and effect sizes between studies. There has been a call for a paradigm shift in modern research (and medicine as a whole) to become separated by sex, including changes in research, medical curricula and residency practice<sup>198</sup>. Taking account of this, research design should examine sexes separately in order to identify potential differences.

#### **8.9.3.2 Implications for future research**

The findings of the current study highlighted a number of potential avenues for future research. Firstly, as birth anthropometric indices only provide a snapshot of average growth in utero, it is not possible to draw conclusions regarding whether specific periods of fetal development may be particularly vulnerable to effects of impaired growth. Future research using ultrasound techniques to measure fetal biometry will allow better tracking of growth across fetal development and identification of the point at which growth falters.

Secondly, based on existing theories of regionally-specific critical periods of neural development<sup>41,199</sup>, it may be hypothesised that neurodevelopmental abilities associated with particular regions (e.g. executive function in the frontal lobe) will be particularly affected when growth impairment coincides with critical periods of growth for that particular region. The continued development and refining of techniques such as fetal MRI and diffusion tensor imaging allow this to be directly tested in future research<sup>200</sup>.

Thirdly, the current thesis only included parent-report measures of attention (the CBCL and SDQ). Parent-report measures behavioural manifestations of attention, which provides no information about the function of attention sub-types (e.g. sustained vs selective attention). As such, future research could test the association between fetal growth and attention development using objective attention tasks (such as a continuous performance task). Further direct assessments of attention is likely to be important for examining the likelihood that growth impaired neonates will go on to develop clinical-level attention difficulties, such as ADHD. ADHD has been shown to lead to a number of adverse outcomes including poor academic performance, anti-social behaviour and substance abuse<sup>201</sup>, and is thus very important for future research.

Fourthly, as previously discussed, a large gap in existing literature in this field is the paucity of research in LMIC samples. The findings of the current thesis identified that associations may differ between HICs and LMICs. As such, it is inappropriate to continue to rely largely on extrapolations from HIC samples to LMIC populations. One of the cohorts which included LMIC samples, the INTERGROWTH-21<sup>st</sup> cohort, however, was designed to include only low-risk mothers. Samples including only low-risk mothers are not representative of the population from which they are drawn. Future research in LMICs should therefore examine mothers across all risk-profiles to understand whether there may be differences.

Finally, the over-reliance on data from HICs is largely due to the quantity of resources, infrastructure and specialised health professionals required to conduct neurodevelopmental assessments. The INTER-NDA which has been developed for use across a range of high-, middle- and low-income settings and validated in this thesis, could be seen as a step in the direction of using a valid instrument for cross-site studies.

### **8.10 Conclusion**

This thesis provided evidence for differential effects of impaired fetal growth on neurodevelopment in childhood. Stunted skeletal growth, evidenced by restricted BL, was associated with poorer attention outcomes in childhood, specifically in females. This association was identified in samples drawn from high-, middle- and low-income countries, which suggest that the association is relatively robust to differential confounding effects. These findings provide support for a sex-specific physiological link between impaired fetal growth and child attention development. Stunted HC and low PI were associated with poor cognitive outcomes in childhood, in both males and females. This association was stronger in LMICs suggesting that confounding structures in these settings (for example maternal and neonatal health and childhood education) may augment the physiological effect of impaired fetal growth on cognitive development. The use of birth anthropometric indices to identify potential risk of poor neurodevelopmental outcomes in childhood may assist in identifying children for further neurodevelopmental assessment, and thus help reduce the loss of neurodevelopmental potential.

## 8.11 References

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## **Appendix I: Supplementary Tables and Figures**

### **Chapter 2**

**Table S2.1. Description of search terms in each database**

| Search element            | Medline                                 | CINAHL                                  | PsychInfo                               | Scopus                                         | WHO Library                               | Dissertation&Theses A&I                   |
|---------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|------------------------------------------------|-------------------------------------------|-------------------------------------------|
| <b>Growth restriction</b> | <b>Thesaurus exploded term</b>          | <b>Thesaurus exploded term</b>          | <b>Thesaurus exploded term</b>          | <b>Thesaurus exploded term</b>                 | <b>Thesaurus exploded term</b>            | <b>Thesaurus exploded term</b>            |
|                           | fetal growth impairment;<br>OR          | fetal growth impairment;<br>OR          | fetal growth impairment;<br>OR          | ALL("fetal growth<br>impairment"); OR          | "fetal growth impairment";<br>OR          | "fetal growth impairment";<br>OR          |
|                           | foetal growth impairment;<br>OR         | foetal growth impairment;<br>OR         | foetal growth impairment;<br>OR         | ALL("foetal growth<br>impairment"); OR         | "foetal growth<br>impairment"; OR         | "foetal growth<br>impairment"; OR         |
|                           | fetal growth restriction; OR            | fetal growth restriction; OR            | fetal growth restriction; OR            | ALL("fetal growth<br>restriction"); OR         | "fetal growth restriction";<br>OR         | "fetal growth restriction";<br>OR         |
|                           | foetal growth restriction;<br>OR        | foetal growth restriction;<br>OR        | foetal growth restriction;<br>OR        | ALL("foetal growth<br>restriction"); OR        | "foetal growth restriction";<br>OR        | "foetal growth restriction";<br>OR        |
|                           | intrauterine growth<br>restriction; OR  | intrauterine growth<br>restriction; OR  | intrauterine growth<br>restriction; OR  | ALL("intrauterine growth<br>restriction"); OR  | "intrauterine growth<br>restriction"; OR  | "intrauterine growth<br>restriction"; OR  |
|                           | fetal growth retardation;<br>OR         | fetal growth retardation;<br>OR         | fetal growth retardation;<br>OR         | ALL( "fetal growth<br>retardation"); OR        | "fetal growth retardation";<br>OR         | "fetal growth retardation";<br>OR         |
|                           | foetal growth retardation;<br>OR        | foetal growth retardation;<br>OR        | foetal growth retardation;<br>OR        | ALL("foetal growth<br>retardation"); OR        | "foetal growth<br>retardation"; OR        | "foetal growth<br>retardation"; OR        |
|                           | intrauterine growth<br>retardation; AND | intrauterine growth<br>retardation; AND | intrauterine growth<br>retardation; AND | ALL("intrauterine growth<br>retardation"); AND | "intrauterine growth<br>retardation"; AND | "intrauterine growth<br>retardation"; AND |
| <b>Outcome</b>            | <b>Thesaurus exploded term</b>          | <b>Thesaurus exploded term</b>          | <b>Thesaurus exploded term</b>          | <b>Thesaurus exploded term</b>                 | <b>Thesaurus exploded term</b>            | <b>Thesaurus exploded term</b>            |
| <b>Phase 1:</b>           | outcome; OR                             | outcome; OR                             | outcome; OR                             | ALL(outcome); OR                               | outcome; OR                               | outcome; OR                               |
|                           | prognosis                               | prognosis                               | prognosis                               | ALL(prognosis)                                 | prognosis                                 | prognosis                                 |
| <b>Phase 2:</b>           | neurodevelopment;                       | neurodevelopment;                       | neurodevelopment;                       | ALL(neurodevelopment);                         | neurodevelopment;                         | neurodevelopment;                         |
| <b>Phase 3:</b>           | cognitive; OR                           | cognitive; OR                           | cognitive; OR                           | ALL(cognitive); OR                             | cognitive; OR                             | cognitive; OR                             |
|                           | cognition; OR                           | cognition; OR                           | cognition; OR                           | ALL(cognition); OR                             | cognition; OR                             | cognition; OR                             |

**Table S2.1. Description of search terms in each database**

| Search element     | Medline         | CINAHL            | PsychInfo       | Scopus               | WHO Library     | Dissertation&Theses A&I        |
|--------------------|-----------------|-------------------|-----------------|----------------------|-----------------|--------------------------------|
|                    | language; OR    | language; OR      | language; OR    | ALL(language); OR    | language; OR    | language; OR                   |
|                    | verbal; OR      | verbal; OR        | verbal; OR      | ALL(verbal); OR      | verbal; OR      | verbal; OR                     |
|                    | hearing; OR     | hearing; OR       | hearing; OR     | ALL(hearing); OR     | hearing; OR     | hearing; OR                    |
|                    | auditory; OR    | auditory; OR      | auditory; OR    | ALL(auditory); OR    | auditory; OR    | auditory; OR                   |
|                    | vision; OR      | vision; OR        | vision; OR      | ALL(vision); OR      | vision; OR      | vision; OR                     |
|                    | visual; OR      | visual; OR        | visual; OR      | ALL(visual); OR      | visual; OR      | visual; OR                     |
|                    | behaviour; OR   | behaviour; OR     | behaviour; OR   | ALL(behaviour); OR   | behaviour; OR   | behaviour; OR                  |
|                    | behaviour; OR   | behaviour; OR     | behaviour; OR   | ALL(behaviour); OR   | behaviour; OR   | behaviour; OR                  |
|                    | temperament; OR | temperament; OR   | temperament; OR | ALL(temperament); OR | temperament; OR | temperament; OR                |
|                    | sleep; OR       | sleep; OR         | sleep; OR       | ALL(sleep); OR       | sleep; OR       | sleep; OR                      |
|                    | motor           | motor             | motor           | ALL(motor)           | motor           | motor                          |
| <b>Search mode</b> | Boolean/phrase  | Boolean/phrase    | Boolean/phrase  |                      |                 |                                |
| <b>Population</b>  | All             | All               | All             |                      |                 |                                |
| <b>Language</b>    | All             | All               | All             | LANGUAGE(ALL)        |                 | All                            |
| <b>Date range</b>  | 1970-2012       | Jan 1970-Dec 2012 | 1970-2012       | PUBYEAR(1970-2012)   |                 | “Specific date range=1970-2012 |

WHO = World Health Organisation

**Table S2.2. Means and standard deviations of standardised mean differences (SMDs) across neurodevelopmental domain, by gestational age at birth**

| Domain    | <35 Weeks GA | ≥35 Weeks GA |
|-----------|--------------|--------------|
| Behaviour | -1.00 (1.01) | -0.47 (0.30) |
| Cognitive | -0.89 (0.70) | -0.52 (0.35) |
| Language  | -0.73 (0.40) | -0.35 (0.25) |
| Motor     | -0.38 (0.51) | -0.46 (0.33) |
| Hearing   | -0.96 (1.18) | -0.36 (0.14) |
| Vision    | -0.34 (0.70) | -0.83 (-)    |
| Sleep     | -            | -0.55 (-)    |
| Overall   | -0.71 (0.29) | -0.51 (0.16) |

**Table S2.3. Means and standard deviations of standardised mean difference (SMDs) across domain, by gestational age at birth, using definition of growth restriction including only those with both abnormal Doppler and small size**

| Domain    | <35 Weeks GA | ≥35 Weeks GA |
|-----------|--------------|--------------|
| Behaviour | -1.09 (0.20) | -0.50 (0.05) |
| Cognitive | -1.03 (0.47) | -0.28 (0.15) |
| Language  | -0.72 (0.53) | -0.19 (0.41) |
| Motor     | -0.95 (0.06) | -0.39 (0.42) |
| Hearing   | -1.63 (0.28) | -            |
| Vision    | 0.03 (0.92)  | -            |
| Sleep     | -            | -            |
| Overall   | -0.90 (0.54) | -0.34 (0.13) |

**Table S2.4. Means and standard deviations of standardised mean differences (SMDs) across neurodevelopmental domain, by gestational age at birth, excluding studies with multiple follow-ups of the same cohort**

| Domain    | <35 Weeks GA | ≥35 Weeks GA |
|-----------|--------------|--------------|
| Behaviour | -1.08 (1.06) | -0.63 (0.23) |
| Cognitive | -0.89 (0.70) | -0.45 (0.39) |
| Language  | -0.73 (0.40) | -0.35 (0.25) |
| Motor     | -0.46 (0.48) | -0.45 (0.34) |
| Hearing   | -0.96 (1.18) | -0.36 (0.14) |
| Vision    | -0.29 (0.86) | -0.83 (-)    |
| Sleep     | -            | -0.55 (-)    |
| Overall   | -0.74 (0.31) | -0.52 (0.17) |

**Table S2.5. Behaviour outcomes by study (≥35 weeks)**

[illegible]



**Table S2.5. Behaviour outcomes by study (≥35 weeks)**

| Study                              | Qual Rating | N IUGR/N Control       | IUGR and/or FCR Definition                                                                                                               | GA (wks) at Measurement | Measurements  | Follow-up Age and Outcome Measure | Significant Findings                                                                                                                                                                                            | IUGR Score M(SD)                                                                                | Control Score M(SD) | Strength of Effects                                                  |
|------------------------------------|-------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|---------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|---------------------|----------------------------------------------------------------------|
| Eixarch et al., 2008               | ***         | 25/100/97 <sup>^</sup> | IUGR = BW <10 <sup>th</sup> percentile and UA-PI >95 <sup>th</sup> percentile. FCR = IUGR as above and MCA-PI<5 <sup>th</sup> percentile | <7 days before delivery | UA-PI, MCA-PI | 2 yrs ASQ                         | Redistributed IUGR group had lower scores in personal-social domain than control group (p=.008). Redistributed IUGR group had lower scores in personal-social domain than non-redistributed IUGR group (p=.049) | Non-Redis = 44.9(26.2)<br>Redis = 42.2(27.6)                                                    | 57.0(26.2)          | Control vs Redis:<br>SMD = 0.55<br>Control vs Non-redis:<br>SMD=0.46 |
| <b>Regression Analysis Studies</b> |             |                        |                                                                                                                                          |                         |               |                                   |                                                                                                                                                                                                                 |                                                                                                 |                     |                                                                      |
| <b>Serial Ultrasound</b>           |             |                        |                                                                                                                                          |                         |               |                                   |                                                                                                                                                                                                                 |                                                                                                 |                     |                                                                      |
| Henrichs et al., 2008              | ***         | 3985 <sup>α</sup>      | Fetal growth = size in late pregnancy – size in mid pregnancy                                                                            | 18-25, ≥25              | HC, AC        | 3 mths MABS                       | Slow growth from mid-pregnancy was significantly associated with decreased infant alertness (p<.001)                                                                                                            | B = -15.6 (-23.8 - -7.31)                                                                       |                     |                                                                      |
| Henrichs et al., 2009              | ***         | 4384 <sup>α</sup>      | Fetal growth = SD of size in late pregnancy – SD of size in mid pregnancy                                                                | <18, 18-25, ≥25         | HC, AC, FL    | 12 mths MIDI                      | Slower growth from mid- to late-pregnancy increased the risk of delayed social (p=.001) and self-help abilities (p=.006)                                                                                        |                                                                                                 |                     | SMD= 0.13                                                            |
| Roza et al., 2008b                 | **          | 3792 <sup>α</sup>      | Latent growth curve modelling used to obtain fetal growth scores. Compared to Generation R study population curve                        | 12.9, 20.5, 30.4        | HC, AC, FL    | 6 mths IBQ-R                      | Fetal growth negatively associated with activity level (p<.01) and duration of orienting (p<.01), however difference did not maintain significance after controlling for maternal variables                     | Activity Level:<br>B= -0.62(-0.89 - -0.35)<br>Duration of orienting:<br>B= -0.53(-0.82 - -0.24) |                     |                                                                      |
| <b>Doppler Velocimetry</b>         |             |                        |                                                                                                                                          |                         |               |                                   |                                                                                                                                                                                                                 |                                                                                                 |                     |                                                                      |
| McCowan et al., 2002               | **          | 220 <sup>α</sup>       | IUGR = AREDFV in UA and BW<10 <sup>th</sup> percentile                                                                                   | <2 wks before delivery  | UA            | 18 mths BRS                       | All children were IUGR. A low BRS score was associated with a birth ponderal index <10 <sup>th</sup> percentile (p<.05), small head size at birth (p<.01), and a greater cord arterial base deficit (p<.01)     |                                                                                                 |                     | SMD=0.48                                                             |

**Table S2.5. Behaviour outcomes by study (≥35 weeks)**

| Study             | Qual Rating | N IUGR/N Control  | IUGR and/or FCR Definition                      | GA (wks) at Measurement | Measurements  | Follow-up Age and Outcome Measure | Significant Findings                                                                                                                                             | IUGR Score M(SD) | Control Score M(SD) | Strength of Effects |
|-------------------|-------------|-------------------|-------------------------------------------------|-------------------------|---------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------------------|---------------------|
| Roza et al., 2008 | ***         | 1135 <sup>a</sup> | FCR based on U/C ratio. U/C ratio = UA-PI/CA-PI | 30                      | UA, ACA, MCA, | 18 mths CBCL                      | Increased U/C ratio ('brain sparing') was significantly positively associated with emotional reactivity, somatic complaints and attentional problems (all p<.05) |                  |                     | SMD = 0.13          |

**Note.** FCR = fetal circulatory redistribution; <sup>a</sup>= IUGR normal MCA-PI/IUGR abnormal MCA-PI/Controls; α = total N; ~ = approximately 7 weeks post-birth; yrs = years; mths = months; UA = umbilical artery; MCA = middle cerebral artery; ACA = Anterior Cerebral Artery; PI = pulsatility index; U/C ratio = umbilical/cerebral ratio; HC = head circumference; AC = abdominal circumference; FL = femur length; BPD = biparietal diameter; RI = resistance index; S/D= systolic/diastolic; BW = birth weight; CI = cephalisation index; AREDV = absent or reverse end-diastolic flow velocity; NEPSY = A Developmental NEuroPSYchological Assessment; MDI = Mental Development Index; CBCL = Child Behaviour Checklist; ASQ = Ages and Stages Questionnaire; MABS = Mother and Baby Scales; MIDI = Minnesota Infant Development Inventory; IBQ-R = Infant Behaviour Questionnaire – Revised; BRS = Behaviour Rating Scale in Bayley Scales of Infant Development; SDQ = Strengths and Difficulties Questionnaire; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias.

**Table S2.6. Cognitive outcomes by study (≥35 weeks)**

| Study                                     | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                                                                                                                                 | GA (wks) at Measurement | Measurements | Follow-up Age and Outcome Measure                     | Significant Findings                                                                                                                                                                                                                                                                                   | IUGR Score M(SD)                                                                                                                 | Control Score M(SD)                                                                                                                  | Strength of Effects                                                                                                                                                  |
|-------------------------------------------|-------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Between Group Studies                     |             |                  |                                                                                                                                                            |                         |              |                                                       |                                                                                                                                                                                                                                                                                                        |                                                                                                                                  |                                                                                                                                      |                                                                                                                                                                      |
| Serial Ultrasound                         |             |                  |                                                                                                                                                            |                         |              |                                                       |                                                                                                                                                                                                                                                                                                        |                                                                                                                                  |                                                                                                                                      |                                                                                                                                                                      |
| Fattal-Valevski et al., 1999 <sup>^</sup> | **          | 85/42            | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile. Redistribution identified by CI >1SD of control M | 20-27                   | HC           | 3 yrs Stanford-Binet                                  | No difference between IUGR group and controls (p>.05).                                                                                                                                                                                                                                                 | 94.9(16.4)                                                                                                                       | 94.9(9.1)                                                                                                                            | IUGR vs controls: SMD=0.00                                                                                                                                           |
| Geva et al., 2006 <sup>^</sup>            | ***         | 123/63           | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile. Redistribution identified by CI >1SD of control M | 20-27                   | HC           | 9 yrs WISC-R95 K-ABC Good-enough-Harris Draw-A-Person | IUGR group scored lower than controls in the WISC-R95 (p<.001); Goodenough-Harris Draw-A-Person test (p<.019); executive function (form fluency p<.001, tower of London p<.014), visual auditory digit span evaluation (p<.001), and K-ABC (decoding p<.043, comprehension p<.006, arithmetic p<.003). | WISC =99.4(13.9)<br>Harris = 94.3(20.4)<br>EF = 95.8(17.3)<br>K-ABC: Dec =95.5(15.4)<br>Comp = 99.7(17.2)<br>Arith = 101.1(17.4) | WISC =107.3(10.5)<br>Harris =101.5(18.0)<br>EF = 103.9(10.9)<br>K-ABC: Dec =102.1(11.7)<br>Comp = 107.3(12.4)<br>Arith = 111.3(12.0) | <b>WISC:</b> SMD=0.65<br><b>Harris:</b> SMD=0.37<br><b>EF:</b> SMD=0.56<br><b>K-ABC dec:</b> SMD=0.48<br><b>K-ABC comp:</b> SMD=0.51<br><b>K-ABC Arith:</b> SMD=0.68 |
| Geva et al., 2006b <sup>18^</sup>         | **          | 110/61           | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile                                                    | 20-27                   | HC           | 9 yrs VADS RAVLT ROCF                                 | IUGR group scored lower than the control group on the ROCF (design copy, immediate incidental recall and delayed incidental recall) (p<.05), and on immediate recall of digit span on VADS (p<.05)                                                                                                     | ROCF: Design Copy = 32.7(19.3)<br>Imm. Recall= 28.0(21.5)<br>Delayed Recall =26.1(20.3)<br>VADS: Immediate Recall=2.2(0.7)       | ROCF: Design Copy =44.1(24.1)<br>Imm. Recall= 37.2(29.7)<br>Delayed Recall =39.0(30.6)<br>VADS: Immediate Recall=2.6(0.5)            | <b>Design Copy:</b> SMD = 0.52<br><b>Imm. Recall:</b> SMD = 0.35<br><b>Delayed Recall:</b> SMD = 0.49<br><b>Immediate Recall (VADS):</b> SMD = 0.69                  |

**Table S2.6. Cognitive outcomes by study (≥35 weeks)**

| Study                             | Qual Rating | N IUGR/N Control      | IUGR and/or FCR Definition                                                                                                                                                                                 | GA (wks) at Measurement      | Measurements | Follow-up Age and Outcome Measure | Significant Findings                                                                                                                                                                                                                                                             | IUGR Score M(SD)                                                                                                                                                                                                    | Control Score M(SD)                                                                          | Strength of Effects                                                                                                                                                                                                                                                                                     |
|-----------------------------------|-------------|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|--------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Harvey et al., 1982               | **          | 10/41/41 <sup>®</sup> | IUGR = weekly growth increment in BPD <5 <sup>th</sup> percentile over ≥2 weeks (compared to normal BPD curves) and BW<10 <sup>th</sup> percentile. IUGR onset divided into pre-26 weeks vs post-26 weeks. | <30 to <2wks before delivery | BPD          | 3-7 yrs McCarthy scales           | IUGR pre-26 weeks had lower scores than controls on perceptual-performance (p<.01), and general cognitive index (p<.02). IUGR pre-26 weeks had lower scores than IUGR post-26 weeks on perceptual-performance (p<.05), quantitative (p<.02) and general cognitive index (p<.05). | McCarthy Scales: Perceptual-Performance: IUGR>26 week = 58.0(10.9) IUGR<26 week = 51.5(7.0) Quantitative: IUGR>26 week = 55.7(8.4) IUGR<26 week = 49.2(6.6) GCI: IUGR>26 week=113.2(16.4) IUGR<26 week=102.9 (11.7) | McCarthy Scales: Perceptual-Performance: 63.5(8.1) Quantitative: 54.0(11.2) GCI: 118.0(12.9) | <b>GCI:</b><br>IUGR<26 vs control: SMD = 1.30<br>IUGR<26 vs IUGR>26 week: SMD = 0.79<br><b>Perceptual Performance:</b><br>IUGR<26 week vs control: SMD = 1.59<br>IUGR<26 vs IUGR>26 week: SMD = 0.71<br><b>Quantitative:</b><br>IUGR<26 vs IUGR>26 week: SMD = 0.86<br>>26 week vs control GCI SMD=0.33 |
| Leitner et al., 2000 <sup>^</sup> | **          | 81/41                 | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile. Redistribution identified by CI >1SD of control M                                                 | 20-27                        | HC           | 6-7 yrs WPPSI                     | IUGR group lower than controls on WPPSI (p<.05)                                                                                                                                                                                                                                  | 101.38(14.1)                                                                                                                                                                                                        | 107.0(13.9)                                                                                  | Effect sizes IUGR vs control SMD = 0.40                                                                                                                                                                                                                                                                 |

**Table S2.6. Cognitive outcomes by study (≥35 weeks)**

| Study                               | Qual Rating | N IUGR/N Control       | IUGR and/or FCR Definition                                                                                                               | GA (wks) at Measurement | Measurements  | Follow-up Age and Outcome Measure | Significant Findings                                                                                                                                                                                                             | IUGR Score M(SD)                                                             | Control Score M(SD)                                                              | Strength of Effects                                                                                                               |
|-------------------------------------|-------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|---------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| Leitner et al., 2005 <sup>19^</sup> | **          | 28/29                  | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile.                                 | 20-27                   | HC            | 6 yrs RAM K-ABC                   | IUGR group lower than controls on correct entrances (p<.05) and time to complete task (p<.05) on RAM. IUGR group scored lower than controls group (p<.001) on K-ABC.                                                             | RAM: Correct/total entrances = 0.33(0.4)<br>Time =71.1(29)<br>K-ABC=9.7(3.1) | RAM: Correct/total entrances = 0.53(0.2)<br>Time = 53.3(27)<br>K-ABC = 12.3(2.6) | <b>RAM IUGR vs Controls:</b><br>Correct Entrances: SMD = 0.63<br>Time: SMD = 0.64<br><b>K-ABC IUGR vs Controls:</b><br>SMD = 0.91 |
| Leitner et al., 2007 <sup>20^</sup> | **          | 123/63                 | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile. FCR= CI >1SD of control M       | 20-27                   | HC            | 9-10 yrs WISC-R95 K-ABC           | IUGR group had lower scores than controls (p<.001) on WISC. Specific subscale differences include memory performance (p<.001) and learning ability (p<.001).IUGR had significantly lower scores than controls (p<.001) on K-ABC. | WISC = 98.39(12.9)                                                           | WISC =107.5(10.4)                                                                | <b>IUGR vs Control:</b><br>SMD = 0.78                                                                                             |
| <b>Doppler Velocimetry</b>          |             |                        |                                                                                                                                          |                         |               |                                   |                                                                                                                                                                                                                                  |                                                                              |                                                                                  |                                                                                                                                   |
| Eixarch et al., 2008                | ***         | 25/100/97 <sup>+</sup> | IUGR = BW <10 <sup>th</sup> percentile and UA-PI >95 <sup>th</sup> percentile. FCR = IUGR as above and MCA-PI<5 <sup>th</sup> percentile | <7 days before delivery | UA-PI, MCA-PI | 2 yrs ASQ                         | IUGR FCR group had lower problem-solving scores than weight-matched controls (p=.04).                                                                                                                                            | Redist: 39.7(26.0)<br>Non-redist: 47.4(27.8)                                 | 49.0(26.8)                                                                       | Redist vs controls<br>SMD = 0.35<br>Non-redist vs controls:<br>SMD=0.06                                                           |

**Table S2.6. Cognitive outcomes by study (≥35 weeks)**

| Study                              | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                               | GA (wks) at Measurement       | Measurements    | Follow-up Age and Outcome Measure | Significant Findings                                                                                                                                                                      | IUGR Score M(SD)     | Control Score M(SD)   | Strength of Effects                   |
|------------------------------------|-------------|------------------|----------------------------------------------------------|-------------------------------|-----------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-----------------------|---------------------------------------|
| Ley et al., 1996                   | **          | 41/105           | IUGR = AREDFV and fetal BPD ≥ 2SD below the mean         | Final measure before delivery | DAo, BPD        | 6.5 yrs WPPSI                     | AREDFV group had significantly lower global IQ than controls (p<.05).                                                                                                                     | 96.0(17.6)           | 102.1(12.2)           | Global IQ IUGR vs Control: SMD = 0.40 |
| McCowan et al., 2002               | **          | 220 <sup>α</sup> | IUGR = AREDFV in UA and BW<10 <sup>th</sup> percentile   | <2 wks before delivery        | UA              | 18 mths BSID-II                   | Mean MDI score was significantly lower in IUGR group than controls (p=.01)                                                                                                                | 95.6(14.5)           | Reference = 100(15)   | IUGR vs Norms: SMD=0.30               |
| <b>Regression Analysis Studies</b> |             |                  |                                                          |                               |                 |                                   |                                                                                                                                                                                           |                      |                       |                                       |
| <b>Serial Ultrasound</b>           |             |                  |                                                          |                               |                 |                                   |                                                                                                                                                                                           |                      |                       |                                       |
| Walker et al., 2006                | **          | 186 <sup>β</sup> | Measurements acquired in early-, mid- and late-gestation | 14, 25, 35                    | HC, BPD, FL, AC | 6-8 yrs RPM<br>Digit Span Forward | Head circumference in early gestation was significantly associated with reasoning ability at age 6-8 yrs, with a significant difference between the lowest and highest quartiles (p=.042) | Lowest HC=15.6(3.87) | Highest HC=18.1(4.04) | Lowest vs highest quartiles: SMD=0.63 |

**Note.** <sup>α</sup>= same cohort; \* = reported in both between-groups and regression analyses. RPM=Raven's Progressive Matrices; \* = IUGR normal MCA-PI/IUGR abnormal MCA-PI/Controls; AoI = Aortic Isthmus; <sup>®</sup> = pre-26 weeks/post-26 weeks/controls; <sup>β</sup> = whole cohort; <sup>€</sup> = AREDFV/Abnormal cerebroplacental ratio/controls; BSID = Bayley Scales of Infant Development; WISC = Wechsler Intelligence Scale for Children; K-ABC = Kaufman Assessment Battery for Children; VADS = Visual Auditory Digit Span; RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey Osterrieth Complex Figure Test; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; RAM = Radial Arm Maze; RPM = Raven's Progressive Matrices; RAKIT = Revisie Amsterdamse Kinder Intelligentietest; BAS = British Abilities Scale; CAT/CLAMS = Clinical Adaptive/Clinical Linguistic Auditory Milestone Age; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias.

**Table S2.7. Language outcomes by studies (≥35 weeks)**

| Study                    | Qual Rating | N IUGR/N Control      | IUGR and/or FCR Definition                                                                                                                                                                                | GA (wks) at Measurement      | Measurements | Follow-up age and Outcome Measure        | Significant Findings                                                                              | IUGR Scores M(SD)                                                            | Control Scores M(SD)                                                 | Strength of Effects                                                                                                   |
|--------------------------|-------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|--------------|------------------------------------------|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| <b>Serial Ultrasound</b> |             |                       |                                                                                                                                                                                                           |                              |              |                                          |                                                                                                   |                                                                              |                                                                      |                                                                                                                       |
| Geva et al., 2006        | ***         | 123/63                | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> Percentile                                                                                                   | 20-27                        | HC           | 9 yrs WISC-R95: Language                 | IUGR group scored lower than controls in vocabulary (p<.019), and verbal problem solving (p<.006) | Vocab = 10.2(3.1)<br>VPS = 98.9(15.3)                                        | Vocab = 11.7(2.8)<br>VPS=104.8(13.1)                                 | <b>Vocab:</b><br>SMD=0.50<br><b>VPS:</b><br>SMD=0.42                                                                  |
| Harvey et al., 1982      | **          | 10/41/41 <sup>®</sup> | IUGR = weekly growth increment in BPD <5 <sup>th</sup> percentile over ≥2 weeks (compared to normal BPD curves) and BW<10 <sup>th</sup> percentile. IUGR onset divided into pre-26 weeks vs post-26 weeks | <30 to <2wks before delivery | BPD          | 3-7 yrs McCarthy Scales: Verbal          | No differences in verbal abilities were identified between any of the groups (p>.05)              | <b>Verbal score:</b><br>Pre-26 week = 53.4(11.4)<br>Post-26 week =56.7(11.6) | Verbal score = 57.5(9.0)                                             | <b>Pre vs Cont:</b><br>SMD=0.40<br><b>Post v Cont:</b><br>SMD=0.29<br><b>Pre v Post:</b><br>SMD=0.08                  |
| Leijon et al., 1980      | **          | 29/47                 | IUGR = BPD 1-2SD from mean confirmed by BW 1-2SD; Severe IUGR = BPD≤2SD from mean confirmed by BW≤2SD; Compared to Swedish standard charts                                                                | 36-birth                     | BPD          | 5, 10, 18 mths Griffith's:Hearing-speech | No differences identified between groups at any follow-ups (p>.05)                                | 5 months: 21.8(2.4)<br>10 months: 43.7(6.7)<br>18 months: Severe = 84.8(8.7) | 5 months: 22.3(2.7)<br>10 months: 46.2(5.3)<br>18 months: 89.4(11.1) | <b>Sev vs Cont:</b><br><b>5 months:</b><br>SMD=0.20<br><b>10 months:</b><br>SMD=0.41<br><b>18 months:</b><br>SMD=0.46 |

**Table S2.7. Language outcomes by studies (≥35 weeks)**

| Study                              | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                                                                                                         | GA (wks) at Measurement | Measurements | Follow-up age and Outcome Measure | Significant Findings                                                            | IUGR Scores M(SD) | Control Scores M(SD) | Strength of Effects  |
|------------------------------------|-------------|------------------|------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------|-----------------------------------|---------------------------------------------------------------------------------|-------------------|----------------------|----------------------|
| Leitner et al., 2007 <sup>^*</sup> | **          | 123/63           | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile. FCR= CI >1SD of control M | 20-27                   | HC           | 9-10 yrs Clinical Assessment      | IUGR were clinically rated as having lower speech and language ability (p<.001) | 85.9(9.6)         | 91.2(5.1)            | SMD=0.63 (0.32-0.94) |

## Doppler Velocimetry

|                      |     |            |                                                                                                                                          |                               |               |                          |                                                                                                                                                                                                                             |                                                                   |                                                          |                                                                                         |
|----------------------|-----|------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|---------------|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Eixarch et al., 2008 | *** | 25/100/97^ | IUGR = UA-PI >95 <sup>th</sup> percentile and BW <10 <sup>th</sup> percentile. FCR = IUGR as above and MCA-PI<5 <sup>th</sup> percentile | <7 days before delivery       | UA-PI, MCA-PI | 2 yrs ASQ: Communication | There was difference in the communication scores of the three groups (p=.01), with Non-FCR highest, followed by controls, then FCR. Furthermore, Non-FCR had significantly higher scores than FCR(p=.006), adjusted for SES | <b>Communication:</b><br>Non-FCR = 67.4(21.6)<br>FCR = 53.1(28.7) | Communication=61.3(25.1)                                 | <b>Non FCR vs Controls:</b><br>SMD=-0.26<br>FCR vs controls<br>SMD=0.30                 |
| Ley et al., 1996     | **  | 41/105     | IUGR = AREDFV and fetal BPD≥ 2SD below the mean                                                                                          | Final measure before delivery | DAo, BPD      | 6.5 yrs WPPSI - VIQ      | AREDFV scored lower (p<.05) than the FEDFV on Verbal IQ. This effect was mirrored between AREDFV and FEDFV children who were all >2SD below the mean fetal weight (p<.05)                                                   | All children VIQ = 95.0(15.7)<br>Subgroup = 94.5(16.3)            | All children VIQ = 102.9(13.2)<br>Subgroup = 102.2(12.9) | <b>FEDFV vs AREDFV VIQ:</b><br>SMD=0.54<br><b>Subgroup FEDFV vs AREDFV:</b><br>SMD=0.52 |

## Regression Analysis Studies

## Serial Ultrasound



**Table S2.7. Language outcomes by studies (≥35 weeks)**

| Study               | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                               | GA (wks) at Measurement | Measurements    | Follow-up age and Outcome Measure       | Significant Findings                                                                                                                               | IUGR Scores M(SD) | Control Scores M(SD) | Strength of Effects |
|---------------------|-------------|------------------|----------------------------------------------------------|-------------------------|-----------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------|---------------------|
| Walker et al., 2006 | **          | 186 <sup>β</sup> | Measurements acquired in early-, mid- and late-gestation | 14, 25, 35              | HC, BPD, FL, AC | 6-8 yrs Peabody Picture Vocabulary Test | No correlation identified between any of the anthropometric measures at any timepoint, and outcomes on the Peabody Picture Vocabulary test (p>.05) | 59.2(16.6)        |                      |                     |

**Note.** <sup>^</sup>= IUGR normal MCA-PI/IUGR abnormal MCA-PI/Controls; <sup>β</sup> = whole cohort; DAo = descending aorta; AREDFV = absent or reverse end-diastolic flow velocity; BSID = Bayley Scales of Infant Development; WISC = Wechsler Intelligence Scale for Children; K-ABC = Kaufman Assessment Battery for Children; VADS = Visual Auditory Digit Span; RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey Osterrieth Complex Figure Test; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; RAM = Radial Arm Maze; RPM = Raven's Progressive Matrices; RAKIT = Revisie Amsterdamse Kinder Intelligentietest; BAS = British Abilities Scale; CAT/CLAMS = Clinical Adaptive/Clinical Linguistic Auditory Milestone Age; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias.

**Table S2.8. Motor outcomes by studies multiple follow-up studies (≥35 weeks)**

| Study                        | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                                                                                                          | GA (wks) at Measurement | Measurements | Follow-up Age and Outcome Measure   | Significant Findings                                                                                                                                                                                                                    | IUGR Scores M(SD)                                | Control Scores M(SD)                             | Strength of Effects       |
|------------------------------|-------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|--------------------------------------------------|---------------------------|
| <b>Between Group Studies</b> |             |                  |                                                                                                                                     |                         |              |                                     |                                                                                                                                                                                                                                         |                                                  |                                                  |                           |
| <b>Serial Ultrasound</b>     |             |                  |                                                                                                                                     |                         |              |                                     |                                                                                                                                                                                                                                         |                                                  |                                                  |                           |
| Fatal-Valevski et al., 1999  | **          | 85/42            | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile. FCR = CI >1SD of control M | 20-27                   | HC           | 3 yrs Neurodevelopmental assessment | IUGR group had a less optimal score compared to control (p<.001), specifically inability to walk up stairs alone, inability to walk on tiptoe, inability to cut with scissors, copy circles and imitate crosses.                        | 89.9(8.0)                                        | 93.2(7.0)                                        | IUGR vs control: SMD=0.44 |
| Leitner et al., 2000         | **          | 81/41            | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile. FCR = CI >1SD of control M | 20-27                   | HC           | 6-7 yrs Neuro Exam                  | IUGR group scored significantly lower on overall motor scores compared to controls (p<.05), in co-ordination, lateralization, presence of associated movements, spatial and graphomotor skills.                                         | <b>Overall % with optimal items = 85.6(11.5)</b> | <b>Overall % with optimal items = 89.2 (6.1)</b> | IUGR vs control: SMD=0.39 |
| Leitner et al., 2007         | **          | 123/63           | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile. FCR = CI >1SD of control M | 20-27                   | HC           | 9-10 yrs Neuro Exam                 | IUGR group scored significantly lower on motor co-ordination (passive and active equilibrium, and time co-ordination performance (p<.05). Muscle tone( both axial and limb) was clinically judged to be lower in the IUGR group (p<.05) | 85.9(9.6)                                        | 91.2(5.1)                                        | SMD=0.63 (0.32-0.94)      |

**Table S2.8. Motor outcomes by studies multiple follow-up studies (≥35 weeks)**

**Table S2.8. Motor outcomes by studies multiple follow-up studies (≥35 weeks)**

[illegible]

**Table S2.8. Motor outcomes by studies multiple follow-up studies (≥35 weeks)**

| Study                 | Qual Rating | N IUGR/N Control  | IUGR and/or FCR Definition                                                | GA (wks) at Measurement | Measurements | Follow-up Age and Outcome Measure | Significant Findings                                                                                                                                                                                                                                                                                                       | IUGR Scores M(SD) | Control Scores M(SD) | Strength of Effects                     |
|-----------------------|-------------|-------------------|---------------------------------------------------------------------------|-------------------------|--------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------|-----------------------------------------|
| Henrichs et al., 2009 | ***         | 4384 <sup>α</sup> | Fetal growth = SD of size in late pregnancy – SD of size in mid pregnancy | <18, 18-25, ≥25         | HC, AC, FL   | 12 mths MIDI                      | Fine motor development was positively associated with fetal head circumference growth rate in early to mid-pregnancy (p=.008), and mid to late-pregnancy (p<.001). Gross motor development was positively associated with growth of estimated fetal weight in mid to late-pregnancy (p=.037) Fine motor and HC in mid-late |                   |                      | Fine motor and HC in mid-late: SMD=0.13 |

**Note.** α = total N; ^ = IUGR normal MCA-PI/IUGR abnormal MCA-PI/Controls; # = REDFV/FEDFV; RI = Resistance index; M-ABC = Movement Assessment Battery for Children; HINE = Hammersmith Infant Neurological Examination; QNST = Quick Neurological Screening Test; BBDS = Best Beginnings Developmental Screen; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias.

**Table S2.9. Vision outcomes by studies (≥35 weeks)**

| Study                        | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                                                                                                                          | GA (wks) at Measurement | Measurements | Follow-up Age and Outcome Measure                    | Significant Findings                                       | IUGR Scores M(SD)                                       | Control Scores M(SD)                                    | Strength of Effects                                     |
|------------------------------|-------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------|------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|
| <b>Between Group Studies</b> |             |                  |                                                                                                                                                     |                         |              |                                                      |                                                            |                                                         |                                                         |                                                         |
| <b>Serial Ultrasound</b>     |             |                  |                                                                                                                                                     |                         |              |                                                      |                                                            |                                                         |                                                         |                                                         |
| Thordstein et al., 2004      | **          | 33/21            | IUGR = EFW >22% below M, compared to Scandinavian prenatal growth chart or if increase in EFW <10% of M between 2 measurements separated by 12 days | BPD, FL                 | >16          | 46 weeks GA <sup>a</sup><br>Visual Evoked Potentials | IUGR group had prolonged latencies to both P peaks (p<.05) | <b>P latency:</b><br>0.1Hz = 143(25)<br>0.3Hz = 146(23) | <b>P latency:</b><br>0.1Hz = 125(18)<br>0.3Hz = 129(21) | <b>0.1 Hz:</b><br>SMD=0.83<br><b>0.3Hz:</b><br>SMD=0.77 |

**Note.**  $\mu$  =  $\approx$  10 wks post birth; EFW = estimated fetal weight; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias.

**Table S2.10. Hearing outcomes by studies (≥35 weeks)**

| Study                        | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                                                                                                                                 | GA (wks) at Measurement | Measurements | Follow-up Age and Outcome Measure                  | Significant Findings                                                        | IUGR Scores M(SD)                                                                                                                          | Control Scores M(SD)                                                          | Strength of Effects                                                                                                                                                                                |
|------------------------------|-------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------|----------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Between Group Studies</b> |             |                  |                                                                                                                                                            |                         |              |                                                    |                                                                             |                                                                                                                                            |                                                                               |                                                                                                                                                                                                    |
| <b>Serial Ultrasound</b>     |             |                  |                                                                                                                                                            |                         |              |                                                    |                                                                             |                                                                                                                                            |                                                                               |                                                                                                                                                                                                    |
| Leijon et al., 1980          | **          | 29/47            | IUGR = BPD 1-2SD from mean confirmed by BW 1-2SD; Severe IUGR = BPD $\leq$ 2SD from mean confirmed by BW $\leq$ 2SD<br>Compared to Swedish standard charts | 36-birth                | BPD          | 5, 10 and 18 mths Griffiths' hearing-speech domain | No difference between IUGR and controls on hearing-speech subscale (p>.05). | 5 months:<br>Severe = 21.8(2.4)<br>10 months:<br>Severe = 43.7(6.7)<br>18 months:<br>Severe IUGR = 84.8(8.7)<br>Moderate IUGR = 84.1(14.4) | 5 months:<br>22.3(2.7)<br>10 months:<br>46.2(5.3)<br>18 months:<br>89.4(11.1) | <b>5 months:</b><br>SMD=0.20<br><b>10 months:</b><br>SMD= <b>0.41</b><br><b>18 months:</b><br><b>Sev vs Cont:</b><br>SMD=0.46<br><b>Mod vs Cont:</b><br>SMD=0.41<br><b>Sev vs Mod:</b><br>SMD=0.06 |

**Note.** FCR = fetal circulatory redistribution; AC = abdominal circumference; BPD = biparietal diameter; UA = umbilical artery; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias.

**Table S2.11. Sleep outcomes by studies (≥35 weeks)**

| Study                        | Qual Rating | N IUGR/N Control | IUGR and/or Redistribution Definition                                                                   | GA (wks) at Measurement | Measurements | Follow-up Age and Outcome Measure | Significant Findings                                                                                                                                                                    | IUGR Scores M(SD)                        | Control Scores M(SD)                     | Strength of Effects                    |
|------------------------------|-------------|------------------|---------------------------------------------------------------------------------------------------------|-------------------------|--------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|------------------------------------------|----------------------------------------|
| <b>Between Group Studies</b> |             |                  |                                                                                                         |                         |              |                                   |                                                                                                                                                                                         |                                          |                                          |                                        |
| <b>Serial Ultrasound</b>     |             |                  |                                                                                                         |                         |              |                                   |                                                                                                                                                                                         |                                          |                                          |                                        |
| Leitner et al., 2002         | *           | 26/47            | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile | 20-27                   | HC           | 4-7 yrs Actigraphy                | IUGR had less true sleep time than controls (p=.03), reflective of less time spent in bed. Other parameters did not differ between groups. Confounds controlled for were age and gender | <b>True sleep time (min) =</b> 498(36.7) | <b>True sleep time (min) =</b> 520(42.8) | <b>True sleep time (min):</b> SMD=0.55 |

**Note.** HC = head circumference; BW = birth weight; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias

Table S2.12. Behaviour outcomes by study (&lt;35 weeks)

| Study                     | Qual Rating | N IUGR/N Control      | IUGR and/or FCR Definition                                                            | GA (wks) at Measurement          | Measurements | Follow-up age and Outcome Measure | Significant Findings                                                                                                                                                                                                                                                                                                                                                    | IUGR Score M(SD)                                   | Control Score M(SD)                                                                                 | Strength of Effects                                                             |
|---------------------------|-------------|-----------------------|---------------------------------------------------------------------------------------|----------------------------------|--------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Between Group Studies     |             |                       |                                                                                       |                                  |              |                                   |                                                                                                                                                                                                                                                                                                                                                                         |                                                    |                                                                                                     |                                                                                 |
| Doppler Velocimetry       |             |                       |                                                                                       |                                  |              |                                   |                                                                                                                                                                                                                                                                                                                                                                         |                                                    |                                                                                                     |                                                                                 |
| Morsing et al., 2011      | **          | 34/34/34 <sup>®</sup> | IUGR defined as BW<2SD below M, compared with Swedish growth standard, and AREDFV.    | Final assessment before delivery | UA           | 5-8 yrs SDQ; Brown's ADD Scales   | The preterm (PT)-IUGR group scored higher than the term (T)-AGA control group on Brown's ADD Scales (p=.004), however those in the PT-AGA group did not differ from the T-AGA control group (p>.05). The PT-IUGR group scored higher than the T-AGA control group on the SDQ (p=.001). No difference identified in the PT-AGA group and the T-AGA control group (p>.05) | Brown's ADD: 51.6(10.7)<br>SDQ: PT-IUGR = 9.6(5.1) | Brown's ADD: PT-AGA = 49.1(11.0)<br>T-AGA = 43.7(8.0)<br>SDQ: PT-AGA = 7.8(4.9)<br>T-AGA = 5.1(4.6) | Brown's ADD Scale PT- IUGR vs T-AGA: SMD=0.84<br>SDQ PT-IUGR vs T-AGA: SMD=0.93 |
| Wienerroither et al, 2001 | **          | 23/23                 | IUGR = AC <10 <sup>th</sup> percentile and AREDFV in UA                               | Dating <20, Doppler until birth  | UA           | 3-8 yrs CBCL                      | No significant difference between IUGR group and control group (p>.05)                                                                                                                                                                                                                                                                                                  | <i>Not stated</i>                                  |                                                                                                     |                                                                                 |
| Padilla et al., 2011      | **          | 20/20                 | IUGR = fetal weight <10 <sup>th</sup> percentile, confirmed at birth and UA- PI >2 SD | <34                              | UA           | 18 mths BSID-III                  | Adaptive behaviour impaired in IUGR group compared to control group (p<.05) (difference did not remain following Bonferroni correction)                                                                                                                                                                                                                                 | 94.78(13.97)                                       | 107.20(12.20)                                                                                       | Control vs IUGR: SMD = 0.95                                                     |
| Scherjon et al., 1998     | *           | 34/62                 | IUGR = U/C ratio > 0.72 (indicates FCR)                                               | Last assessment before delivery  | UA, MCA      | 3 yrs Parental Questionnaire      | FCR infants had a higher level of activity (in the abnormal range) compared to control infants, however the level did not reach statistical significance (p=.08). Chi-square=3.14                                                                                                                                                                                       |                                                    |                                                                                                     | SMD=0.37(-0.04-0.77)                                                            |



**Table S2.12. Behaviour outcomes by study (<35 weeks)**

| Study                              | Qual Rating | N IUGR/N Control     | IUGR and/or FCR Definition                          | GA (wks) at Measurement         | Measurements | Follow-up age and Outcome Measure | Significant Findings                                                                                                         | IUGR Score M(SD)                                    | Control Score M(SD)                                | Strength of Effects                               |
|------------------------------------|-------------|----------------------|-----------------------------------------------------|---------------------------------|--------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------|---------------------------------------------------|
| Valcamonico et al., 2007           | *           | 43/15                | IUGR = UA-PI > 2SD from M and BW <1000g             | Last assessment before delivery | UA           | 2 yrs Neuro Exam                  | 15% of controls had minor or major neurological sequelae, whereas 41% of IUGR group had minor or major neurological sequelae |                                                     |                                                    | SMD=1.23(0.07-2.38)                               |
| Schreuder et al., 2002             | **          | 9/27/40 <sup>μ</sup> | IUGR = REDFV                                        | Last assessment before delivery | UA           | 5-12 yrs SDQ                      | REDFV group scored higher than FEDFV on hyperactivity (p=.015) and peer problems (p=.028)                                    | Hyperactivity: 5.9 (1.0)<br>Peer Problems: 4.3(1.0) | Hyperactivity: 3.0(1.0)<br>Peer Problems: 2.1(0.4) | Hyperactivity: SMD=2.9<br>Peer Problems: SMD=2.89 |
| <b>Regression Analysis Studies</b> |             |                      |                                                     |                                 |              |                                   |                                                                                                                              |                                                     |                                                    |                                                   |
| <b>Doppler Velocimetry</b>         |             |                      |                                                     |                                 |              |                                   |                                                                                                                              |                                                     |                                                    |                                                   |
| Van den Broek et al., 2010         | **          | 89 <sup>^</sup>      | IUGR = FGR<0.80. Redistribution = U/C ratio > 0.72. | Last assessment before delivery | UA, MCA      | 11 yrs CBCL                       | FGR is predictive of internalizing score on the CBCL (p=.008), whereas U/C ratio was not                                     |                                                     |                                                    | SMD= 0.75                                         |

**Note.** € = ≈8 weeks post birth; ¥=abnormal MCA/normal MCA/controls; μ = REDFV/AEDFV/FEDFV; ^ = whole cohort; U/C ratio = umbilical PI/cerebral PI; FGR = fetal growth ratio (observed BW/expected BW); NEPSY = A Developmental NEuroPSYchological Assessment; MDI = Mental Development Index; CBCL = Child Behaviour Checklist; ASQ = Ages and Stages Questionnaire; MABS = Mother and Baby Scales; MIDI = Minnesota Infant Development Inventory; IBQ-R = Infant Behaviour Questionnaire – Revised; BRS = Behaviour Rating Scale in Bayley Scales of Infant Development; SDQ = Strengths and Difficulties Questionnaire; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias

**Table S2.13. Cognitive outcomes by study (<35 weeks)**

| Study                            | Qual Rating | N IUGR/N Control     | IUGR and/or FCR Definition                                                                                                                                                                         | GA (wks) at Measurement | Measurements | Follow-up Age and Outcome Measure | Significant Findings                                                                                                                                                                   | IUGR Score M(SD)                                                  | Control Score M(SD)                                             | Strength of Effects                                                                                  |
|----------------------------------|-------------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| <b>Between Group Studies</b>     |             |                      |                                                                                                                                                                                                    |                         |              |                                   |                                                                                                                                                                                        |                                                                   |                                                                 |                                                                                                      |
| <b>Serial Ultrasound</b>         |             |                      |                                                                                                                                                                                                    |                         |              |                                   |                                                                                                                                                                                        |                                                                   |                                                                 |                                                                                                      |
| Bassan et al., 2011 <sup>^</sup> | **          | 114/193 <sup>y</sup> | IUGR = late mid-second-third trimester, growth restriction confirmed by BW <10 <sup>th</sup> percentile, according to Israeli percentile curves. Redistribution identified by CI >1SD of control M | 20-27                   | HC           | BSID-II (2yrs) WPPSI (6yrs)       | No difference identified between groups at 2yrs on MDI scores (p=0.68), or at 6 yrs on IQ scores (p=0.81)                                                                              | BSID= 98.9(17.5) WPPSI = 104.3(15.2)                              | BSID=97.66(20.4) WPPSI =104.9(16.5)                             | MDI Preterm vs Term: SMD=-0.065                                                                      |
| <b>Doppler Velocimetry</b>       |             |                      |                                                                                                                                                                                                    |                         |              |                                   |                                                                                                                                                                                        |                                                                   |                                                                 |                                                                                                      |
| Scherjon et al., 2000            | **          | 28/45                | FCR = U/C ratio >0.725                                                                                                                                                                             | <7 days before delivery | UA, MCA      | 5 yrs RAKIT                       | FCR group scored lower than control group on overall RAKIT score (p<.02), and the disk subtest score (p<.02), and had a significantly higher number with cognitive impairment (p=.003) | <b>Overall Score = 87(16)</b><br><b>Disk Subtest Score= 11(6)</b> | <b>Overall Score =96(17)</b><br><b>Disk Subtest Score=14(4)</b> | <b>Overall Score:</b><br>SMD=0.55<br>Effect size<br>r=0.26<br><b>Disk Subtest Score:</b><br>SMD=0.59 |
| Fouron et al., 2001              | *           | 30/14                | IUGR = retrograde Aol flow, UA-PI>95 <sup>th</sup> percentile and BW≤2SD for GA                                                                                                                    | <2 wks before delivery  | Aol, UA      | 2-4 yrs Griffiths Test            | No difference between those with FEDFV and those with AREDFV on neurodevelopmental socres                                                                                              | Non-Optimal Scores: AREDFV=8/15                                   | Non-Optimal Scores: FEDFV=16/29                                 | SMD=0.04                                                                                             |

**Table S2.13. Cognitive outcomes by study (<35 weeks)**

| Study                  | Qual Rating | N IUGR/N Control      | IUGR and/or FCR Definition                                                                                                                                                    | GA (wks) at Measurement | Measurements          | Follow-up Age and Outcome Measure                                        | Significant Findings                                                                                                                                                                                          | IUGR Score M(SD)                                                                                                                                                                                                               | Control Score M(SD)                                                                                                                    | Strength of Effects                                                                           |
|------------------------|-------------|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-----------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Leppanen et al., 2010  | **          | 16/54                 | IUGR = UA-PI >95 <sup>th</sup> percentile. FCR = UA-PI/MCA-PI >95 <sup>th</sup> percentile                                                                                    | <7days before delivery  | UA, MCA, DAo, AoI, DV | 2 yrs BSID-II                                                            | Abnormal UA-PI compared to normal UA-PI had lower MDI (p=.04), as did abnormal UA-PI/MCA-PI ratio (p=.003), as did DAo-PI/MCA-PI ratio (p=.02), as did DAo-PI (p=.03)                                         | Abnormal UA/MCA = 94.1(16.8)                                                                                                                                                                                                   | Normal UA/MCA = 106.2(12.7)                                                                                                            | <b>Abnormal vs Normal UA-PI/MCA-PI:</b><br>SMD=0.81                                           |
| Kutschera et al., 2002 | **          | 16/15/31 <sup>€</sup> | IUGR = AREDFV in UA (AREDFV group) and BW sig lower than controls. FCR = increased UA-PI, decreased MCA-PI or increased U/C ratio (ABF group) and BW sig lower than controls. | 25-40                   | UA, MCA               | 3-6 yrs K-ABC; Snijders-Oomen Scale for Young Children; Man Drawing Test | The AREDFV scored significantly lower than controls in all subtests of the K-ABC (p<.001) and Snijders-Oomen (p<.001) but not the Man Drawing Test. No significant difference between the ARED and ABF group. | <b>K-ABC M(SD)(Range):</b><br><b>MPC:</b><br>AREDFV=82(4)(74-98)<br>ABF=84(5.75)(71-94)<br><b>SON M(Range):</b><br><b>Mosaic:</b><br>AREDF=7.4(6-11)<br>ABF=8(6-11)<br><b>Combination:</b><br>AREDF=8.4(5-12)<br>ABF=8.6(4-11) | <b>K-ABC M(Range):</b><br>MPC = 99(10)(71-111)<br>AS =95(70-108)<br><b>SON M(Range):</b><br>Mosaic =9.2(7-11)<br>Combination =10(7-12) | <b>AREDFV vs Controls:</b><br>MPC:<br>SMD=2.23<br><b>ABF vs Controls:</b><br>MPC:<br>SMD=1.83 |
| Padilla et al., 2011   | **          | 20/20                 | IUGR = fetal weight below 10 <sup>th</sup> percentile, confirmed at birth and UA- PI >2 SD                                                                                    | <34                     | UA                    | 18 mths BSID-III                                                         | No significant difference between IUGR and control group on cognitive scale of BSID (p=.120)                                                                                                                  | 100.83(9.27)                                                                                                                                                                                                                   | 108.67(12.88)                                                                                                                          | IUGR vs controls:<br>SMD = 0.70<br>Control = 0.33                                             |

**Table S2.13. Cognitive outcomes by study (<35 weeks)**

| Study                      | Qual Rating | N IUGR/N Control      | IUGR and/or FCR Definition                                              | GA (wks) at Measurement          | Measurements | Follow-up Age and Outcome Measure | Significant Findings                                                                                                                                                                                     | IUGR Score M(SD)                                                                                                                   | Control Score M(SD)                                                                                                 | Strength of Effects                                                                                                                                                        |
|----------------------------|-------------|-----------------------|-------------------------------------------------------------------------|----------------------------------|--------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wienerroither et al., 2001 | **          | 23/23                 | IUGR =AREDFV in UA and AC <10 <sup>th</sup> percentile                  | Dating <20, Doppler until birth  | UA           | 3-8 yrs K-ABC                     | IUGR group scored significantly lower than controls on sequential processing scale (p<.001), simultaneous processing scale (p<.025), mental processing composite (p<.025) and achievement scale (p<.005) | SEPS = 84.4(11.7)<br>SIPS = 89.8(11.7)<br>MPC = 86.7(9.6)<br>AS = 82(16.3)                                                         | SEPS = 94.5(11.7)<br>SIPS = 97.2(11.7)<br>MPC = 95.5(9.6)<br>AS = 96(16.3)                                          | IUGR vs controls:<br>SEPS SMD=0.86<br>SIPS SMD=0.63<br>MPC SMD=0.92<br>AS SMD=0.86                                                                                         |
| Morsing et al., 2011       | **          | 34/34/34 <sup>®</sup> | IUGR = AREDFV and BW<2SD below M, compared with Swedish growth standard | Final assessment before delivery | UA           | 5-8 yrs WPPSI or WISC             | PT-IUGR had lower FSIQ (p=.007) than PT-AGA. PT-IUGR had lowerPIQ (p<.001) and FSIQ (p<.001) than T-AGA.                                                                                                 | PIQ =79.3(16.0)<br>FSIQ =78.9(16.6)                                                                                                | <b>PIQ:</b><br>PT-AGA =87.2(17.2)<br>T-AGA =104.7(16.0)<br><b>FSIQ:</b><br>PT-AGA =90.1(14.2)<br>T-AGA =102.9(13.2) | <b>PT-IUGR vs PT-AGA:</b><br><b>FSIQ:</b><br>SMD=0.73<br><b>PT-IUGR vs T-AGA:</b><br><b>FSIQ:</b><br>SMD=1.60<br><b>PIQ:</b> SMD=1.59                                      |
| Schreuder et al., 2002     | **          | 9/27/40 <sup>u</sup>  | IUGR = REDFV                                                            | Last assessment before delivery  | UA           | 5-12 yrs BAS                      | REDFV had lower General Conceptual Ability than FEDFV (p=.049) and AEDFV (p=.048), as well as Spatial/Pictorial ability than FEDFV (p=.023) and AEDFV (p=.025).                                          | <b>GCA:</b><br>AEDFV = 101.1(15.2)<br>REDFV = 87.7 (22.1)<br><b>Spatial/Pictorial:</b><br>AEDFV = 96.2(15.2)<br>REDFV = 80.7(21.5) | <b>GCA</b> = 101.0(12.3)<br><b>Spatial/Pictorial</b> =96.3(17.0)                                                    | <b>GCA REDFV vs FEDFV:</b><br>SMD=0.74<br><b>REDFV vs AEDFV:</b><br>SMD=0.71<br><b>Spatial/Pictorial REDFV vs FEDFV:</b><br>SMD=0.81<br><b>REDFV vs AEDFV:</b><br>SMD=0.83 |

**Table S2.13. Cognitive outcomes by study (<35 weeks)**

| Study                      | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                                                            | GA (wks) at Measurement         | Measurements | Follow-up Age and Outcome Measure | Significant Findings                                                                                                                                                                                                                                             | IUGR Score M(SD)                                                                                                                                                      | Control Score M(SD)                                                                                                                                                         | Strength of Effects                                                               |
|----------------------------|-------------|------------------|---------------------------------------------------------------------------------------|---------------------------------|--------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Vossbeck et al., 2001      | **          | 16/16            | IUGR = AREDFV in UA and BW < 10 <sup>th</sup> percentile                              | Last assessment before delivery | UA           | 13-91 mths<br>BSID-II; K-ABC      | AREDFV had lower MDI on BSID (p=.03) or MPC ON K-ABC (p=.028) than controls (overall p=.005).                                                                                                                                                                    | <b>Medians (Min-Max):</b><br><b>MDI</b> =76.5(50-93)<br>M(SD)=74(10.75)<br><b>MPC</b> =57(47-89)<br>M(SD)=62.5(11.5)<br><b>Overall</b> =75(47-93)<br>M(SD)=72.5(11.5) | <b>Medians (Min-Max):</b><br><b>MDI</b> =98(76-111)<br>M(SD)=95.75(8.75)<br><b>MPC</b> =98(58-104)<br>M(SD)=89.5(11.5)<br><b>Overall</b> = 87(58-111)<br>M(SD)=85.75(13.25) | <b>MDI:</b><br>SMD=2.22<br><b>MPC:</b><br>SMD=2.35<br><b>Overall:</b><br>SMD=1.07 |
| Padilla et al., 2010       | ***         | 37/36            | IUGR = UA-PI>2SD and ultrasound EFW <10 <sup>th</sup> percentile, confirmed at birth. | <34                             | UA, EFW      | 12 mths<br>BSID-II                | No differences between IUGR and control group in MDI (p>.05)                                                                                                                                                                                                     | <b>MDI</b> = 98.8(9.0)                                                                                                                                                | <b>MDI</b> =98.4(13.1)                                                                                                                                                      | <b>MDI:</b><br>SMD=0.04                                                           |
| <b>Regression Analysis</b> |             |                  |                                                                                       |                                 |              |                                   |                                                                                                                                                                                                                                                                  |                                                                                                                                                                       |                                                                                                                                                                             |                                                                                   |
| <b>Doppler Velocimetry</b> |             |                  |                                                                                       |                                 |              |                                   |                                                                                                                                                                                                                                                                  |                                                                                                                                                                       |                                                                                                                                                                             |                                                                                   |
| Torrance et al., 2010      | **          | 71^              | IUGR = BW<10 <sup>th</sup> percentile and UA-PI > 2SD from M                          | <7 days before delivery         | UA, MCA      | 18-24 mths<br>Griffiths, BSID-II  | A test score more than 1 SD lower than the population M at 2 yrs was predicted by BW <2.3 <sup>rd</sup> percentile (p<.01), a UA pH of <7.00 (p<.001), and the presence of placental villitis (p<.05). Primiparity reduced the risk of a low test score (p<.05). |                                                                                                                                                                       |                                                                                                                                                                             | SMD=0.76                                                                          |

**Table S2.13. Cognitive outcomes by study (<35 weeks)**

| Study | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition | GA (wks) at Measurement | Measurements | Follow-up Age and Outcome Measure | Significant Findings | IUGR Score M(SD) | Control Score M(SD) | Strength of Effects |
|-------|-------------|------------------|----------------------------|-------------------------|--------------|-----------------------------------|----------------------|------------------|---------------------|---------------------|
|-------|-------------|------------------|----------------------------|-------------------------|--------------|-----------------------------------|----------------------|------------------|---------------------|---------------------|

**Note.** EFW = estimated fetal weight; ® = IUGR/matched preterm AGA/term AGA; µ = REDFV/AEDFV/FEDFV; ^ = whole cohort; BSID = Bayley Scales of Infant Development; WISC = Wechsler Intelligence Scale for Children; K-ABC = Kaufman Assessment Battery for Children; VADS = Visual Auditory Digit Span; RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey Osterrieth Complex Figure Test; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; RAM = Radial Arm Maze; RPM = Raven's Progressive Matrices; RAKIT = Revisie Amsterdamse Kinder Intelligentietest; BAS = British Abilities Scale; CAT/CLAMS = Clinical Adaptive/Clinical Linguistic Auditory Milestone Age; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias.

**Table S2.14. Language outcomes by study (<35 weeks)**

| Study                        | Qual Rating | N IUGR/N Control     | IUGR and/or FCR Definition                                                 | GA (wks) at Measurement         | Measurements | Follow-Up ages and Outcome Measure | Significant Findings                                                                                                                                                                                                                                                                                                             | IUGR Scores M(SD)                                                                                                                     | Control Scores M(SD)                                                                                                               | Strength of Effects                                       |
|------------------------------|-------------|----------------------|----------------------------------------------------------------------------|---------------------------------|--------------|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| <b>Between Group Studies</b> |             |                      |                                                                            |                                 |              |                                    |                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                       |                                                                                                                                    |                                                           |
| <b>Doppler Velocimetry</b>   |             |                      |                                                                            |                                 |              |                                    |                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                       |                                                                                                                                    |                                                           |
| Scherjon et al., 1998        | *           | 34/62                | IUGR = U/C ratio > 0.72 (indicates FCR)                                    | Last assessment before delivery | 3 yrs        | Neuro. Exam                        | No differences found between raised and normal U/C ratio in the use of pronoun 'I', or the comprehensibility of infants speech for strangers. Passive understanding of language did not differ between groups (p>.05). A tendency was seen in the raised U/C ratio, a tendency was seen to use fewer words in a sentence (p=.09) | Pronoun I (%n) =85%<br>Comprehensibility (%n) =85.3%<br>Parent rating as adequate (%n) = 92.7%<br>Use fewer than 3 words (%n) = 20.6% | Pronoun I (%n) =85%<br>Comprehensibility (%n) =91.8%<br>Parent rating as adequate (%n) =96.5%<br>Use fewer than 3 words (%n) =6.7% | SMD=0.36(-0.36-1.08)                                      |
| Padilla et al., 2011         | **          | 20/20                | IUGR =UA-PI > 2SD and FW< 10 <sup>th</sup> percentile, confirmed at birth. | <34                             | UA           | 18 mths BSID-III                   | No difference identified in overall language score (p=.87), receptive communication (p=.95) or expressive communication (p=.94) between any groups                                                                                                                                                                               | <b>Language scores =</b> 92.72(12.96)                                                                                                 | <b>Language scores:</b> PT-AGA = 94.73(16.57)<br>T-AGA = 95.07(13.36)                                                              | <b>IUGR vs PT:</b> SMD=0.14<br><b>IUGR vs T:</b> SMD=0.18 |
| Valcamonico et al., 2007     | *           | 43/15                | IUGR = UA-PI > 2SD from M and BW <1000g                                    | Last assessment before delivery | UA           | 2 yrs Neuro. Exam                  | 15% of controls had minor or major neurological sequelae, whereas 41% of IUGR group had minor or major neurological sequelae                                                                                                                                                                                                     |                                                                                                                                       |                                                                                                                                    | SMD=1.23(0.07-2.38)                                       |
| Schreuder et al., 2002       | **          | 9/27/40 <sup>u</sup> | IUGR = REDFV                                                               | Last assessment before delivery | UA           | 5-12 yrs BAS – Verbal scale        | No difference between groups on verbal ability (p>.05)                                                                                                                                                                                                                                                                           | Absent = 103.8(17.69)<br>Reversed = 90.2 (26.7)                                                                                       | 102.5(13.9)                                                                                                                        | <b>Rev v Control:</b> SMD=0.58                            |

**Table S2.14. Language outcomes by study (<35 weeks)**

| Study                      | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                                                                      | GA (wks) at Measurement       | Measurements | Follow-Up ages and Outcome Measure | Significant Findings                                                                 | IUGR Scores M(SD) | Control Scores M(SD) | Strength of Effects                      |
|----------------------------|-------------|------------------|-------------------------------------------------------------------------------------------------|-------------------------------|--------------|------------------------------------|--------------------------------------------------------------------------------------|-------------------|----------------------|------------------------------------------|
| <b>Regression Analysis</b> |             |                  |                                                                                                 |                               |              |                                    |                                                                                      |                   |                      |                                          |
| <b>Doppler Velocimetry</b> |             |                  |                                                                                                 |                               |              |                                    |                                                                                      |                   |                      |                                          |
| Baschat et al., 2009       | *           | 72 <sup>^</sup>  | IUGR = Elevated UA-PI and AC < 5 <sup>th</sup> percentile. Elevation of DV-PI > 2 SD = abnormal | Final measure before delivery | UA, MCA, DV  | 2 yrs CAT/CLAMS                    | Neither abnormal DV nor UA-REDFV was associated with adverse speech outcomes (p>.05) |                   |                      | <b>DV and Motor Outcome:</b><br>SMD=0.75 |

**Note.**  $\mu$  = REDFV/AEDFV/FEDFV ; <sup>^</sup>=whole cohort; BSID = Bayley Scales of Infant Development; WISC = Wechsler Intelligence Scale for Children; K-ABC = Kaufman Assessment Battery for Children; VADS = Visual Auditory Digit Span; RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey Osterrieth Complex Figure Test; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; RAM = Radial Arm Maze; RPM = Raven's Progressive Matrices; RAKIT = Revisie Amsterdamse Kinder Intelligentietest; BAS = British Abilities Scale; CAT/CLAMS = Clinical Adaptive/Clinical Linguistic Auditory Milestone Age; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias.



**Table S2.15. Motor outcomes by study (<35 weeks)**

| Study                        | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                                                                 | GA (wks) at Measurement         | Measurements          | Follow-up Age and Outcome Measure                                    | Significant Findings                                                                                                                                                                                 | IUGR Scores M(SD)               | Control Scores M(SD)            | Strength of Effect    |
|------------------------------|-------------|------------------|--------------------------------------------------------------------------------------------|---------------------------------|-----------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------|-----------------------|
| <b>Between Group Studies</b> |             |                  |                                                                                            |                                 |                       |                                                                      |                                                                                                                                                                                                      |                                 |                                 |                       |
| <b>Doppler Velocimetry</b>   |             |                  |                                                                                            |                                 |                       |                                                                      |                                                                                                                                                                                                      |                                 |                                 |                       |
| Fouron et al., 2001          | *           | 30/14            | IUGR = retrograde Aol flow, UA-PI>95 <sup>th</sup> percentile and BW≤2SD for GA            | <2 wks before delivery          | Aol, UA               | 2-4 yrs Griffiths Test: Locomotor and hand-eye subsets; Neuro Exam   | No difference between those with FEDFV and those with AREDFV on neurodevelopmental socres                                                                                                            | Non-Optimal Scores: AREDFV=8/15 | Non-Optimal Scores: FEDFV=16/29 | SMD=0.04 (-0.65-0.73) |
| Kok et al., 2007             | **          | 31/58            | FCR = U/C ratio >0.72                                                                      | Last assessment before delivery | UA, MCA               | 11yrs Beery-Buktenica Visual-Motor index; Motor Accuracy Test; M-ABC | No difference identified in any of the motor tests- Beery-Buktenica (p=.882); Motor accuracy test (p=.210); Catching a ball (p=.236); throw11ing a ball (p=.617) between normal and raised U/C ratio |                                 |                                 | SMD=0.28(0.16-0.72)   |
| Leppanen et al., 2010        | **          | 16/54            | IUGR = UA-PI >95 <sup>th</sup> percentile. FCR = UA-PI/MCA-PI >95 <sup>th</sup> percentile | <7days before delivery          | UA, MCA, DAo, Aol, DV | 2 yrs HINE                                                           | No difference between the abnormal and normal U/C ratio infants on HINE (p>.05)                                                                                                                      | 73.4(2.9)                       | 74.0(3.7)                       | SMD=0.18              |

**Table S2.15. Motor outcomes by study (<35 weeks)**

| Study                 | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                                                                                                      | GA (wks) at Measurement         | Measurements | Follow-up Age and Outcome Measure | Significant Findings                                                                                                                                                                                                | IUGR Scores M(SD)                                                 | Control Scores M(SD)                                                                                                                         | Strength of Effect                                                                                |
|-----------------------|-------------|------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------|--------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Padilla et al., 2010  | ***         | 37/36            | Doppler velocimetry and serial ultrasound. IUGR = UA-PI>2SD and ultrasound EFW <10 <sup>th</sup> percentile, confirmed at birth | <34                             | UA, EFW      | 12 mths BSID-II                   | No difference between groups on PDI (gross and fine motor skills) (p>.05).                                                                                                                                          | 98.8(9.0)                                                         | 98.4(13.1)                                                                                                                                   | SMD=0.04                                                                                          |
| Padilla et al., 2011  | **          | 20/20            | IUGR = UA-PI > 2SD and fetal weight below 10 <sup>th</sup> percentile, confirmed at birth.                                      | <34                             | UA           | 18 mths BSID-III                  | Three groups – preterm IUGR; preterm AGA and term AGA. Preterm IUGR group significantly lower scores than term AGA on overall motor (p<.05) and fine motor (p<.05). No significant differences between other groups | <b>Overall motor</b> = 93.7(17.3)<br><b>Fine motor</b> = 8.8(3.1) | <b>Overall motor:</b><br>Preterm-AGA=102.2(9.6)<br>Term-AGA=110.0(17.2)<br><b>Fine motor:</b><br>Preterm-AGA=10.3(2.0)<br>Term-AGA=11.9(2.6) | <b>Preterm IUGR vs term AGA:</b><br><b>Overall Motor:</b> SMD=0.94<br><b>Fine Motor:</b> SMD=1.09 |
| Scherjon et al., 1998 | *           | 34/62            | IUGR = U/C ratio > 0.72 (indicates FCR)                                                                                         | Last assessment before delivery | UA, MCA      | 3 yrs Neuro Exam                  | No difference between normal and raised U/C groups in number of children classified as normal, mildly abnormal or abnormal (p=0.23) on fine prehension, sitting, crawling, standing or walking                      |                                                                   |                                                                                                                                              | SMD=0.35(-0.77-0.07)                                                                              |

**Table S2.15. Motor outcomes by study (<35 weeks)**

**Table S2.15. Motor outcomes by study (<35 weeks)**

| Study                | Qual Rating | N IUGR/N Control | IUGR and/or FCR Definition                                                                       | GA (wks) at Measurement | Measurements                  | Follow-up Age and Outcome Measure | Significant Findings                                            | IUGR Scores M(SD) | Control Scores M(SD) | Strength of Effect                        |
|----------------------|-------------|------------------|--------------------------------------------------------------------------------------------------|-------------------------|-------------------------------|-----------------------------------|-----------------------------------------------------------------|-------------------|----------------------|-------------------------------------------|
| Baschat et al., 2009 | *           | 72 <sup>^</sup>  | IUGR = AC < 5 <sup>th</sup> percentile and elevated UA-PI.<br>Elevation of DV-PI>2 SD = abnormal | UA, MCA, DV             | Final measure before delivery | 2 yrs BBDS                        | Abnormal DV was associated with abnormal motor outcome (p=.009) |                   |                      | <b>DV and Motor Outcome:</b><br>SMD= 0.75 |

**Note.** DV = Ductus Venosus; <sup>^</sup>=whole cohort;  $\beta$  =  $\approx$ 8 wks post birth ;  $\text{¥}$  = Abnormal MCA/Normal MCA/Controls;  $\mu$  = REDFV/AEDFV/FEDFV; M-ABC = Movement Assessment Battery for Children; HINE = Hammersmith Infant Neurological Examination; QNST = Quick Neurological Screening Test; BBDS = Best Beginnings Developmental Screen; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias

**Table S2.16. Vision outcomes by study (<35 weeks)**

| Study                        | Qual Rating | N IUGR/N Control     | IUGR and/or FCR Definition               | GA (wks) at Measurement         | Measurements | Follow-up Age and Outcome Measure        | Significant Findings                                                                                                                | IUGR Scores M(SD)                                                           | Control Scores M(SD)                                  | Strength of Effects   |
|------------------------------|-------------|----------------------|------------------------------------------|---------------------------------|--------------|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------|-----------------------|
| <b>Between Group Studies</b> |             |                      |                                          |                                 |              |                                          |                                                                                                                                     |                                                                             |                                                       |                       |
| <b>Doppler Velocimetry</b>   |             |                      |                                          |                                 |              |                                          |                                                                                                                                     |                                                                             |                                                       |                       |
| Kok et al., 2007             | **          | 31/58                | FCR = U/C ratio >0.72                    | Last assessment before delivery | UA, MCA      | 11 yrs Orthoptic and Ophthalmologic Exam | Difference detected only in history of occlusion (p=.04) between abnormal and normal U/C ratio.                                     | History of Occlusion n(%) = 9.0(29.0)                                       | History of Occlusion n(%) =6.0(10.3)                  | SMD=0.46(0.02-0.91)   |
| Scherjon et al., 1996        | **          | 34/56                | IUGR = FGR <0.75. FCR = U/C ratio >0.725 | Last assessment before delivery | UA, MCA      | 6 mths Visual Evoked Potentials          | FCR group show nearly no decline in P2 latency during studied period, whereas normal group showed significant decline               | 5.6(20.3)ms                                                                 | 26.6(42.6)ms                                          | SMD=0.63              |
| Valcamonico et al., 2007     | *           | 43/15                | IUGR = UA-PI > 2SD from M and BW <1000g  | Last assessment before delivery | UA           | 2 yrs Neuro Exam using Touwen protocol   | 31% of FEDFV group exhibited retinopathy of prematurity, whereas only 11.9% of AREFV group exhibited the same                       |                                                                             |                                                       | SMD=-0.68(-1.42-0.06) |
| Schreuder et al., 2002       | **          | 9/27/40 <sup>u</sup> | IUGR = REDFV                             | Last assessment before delivery | UA           | 5-12 yrs Snellen acuity testing          | Higher proportion of children in the REDFV group with severe acuity loss, than in the AEDFV group (p=.014) or FEDFV group (p=.047). | <b>% of children with severe acuity loss:</b><br>REDFV = 56%<br>AEDFV = 11% | <b>% of children with severe acuity loss =</b><br>19% | SMD=0.93(0.08-1.79)   |

**Note.** β = ≈8 wks post birth ; ¥ = Abnormal MCA/Normal MCA/Controls; μ = REDFV/AEDFV/FEDFV; ^ = whole cohort; FGR = fetal growth ratio (expected BW/observed BW); \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias

Table S2.17. Hearing outcomes by study (&lt;35 weeks)

| Study                               | Qual Rating | N IUGR/N Control     | IUGR and/or FCR Definition                                                                     | GA (wks) at Measurement         | Measurements                  | Follow-up Age and Outcome Measure        | Significant Findings                                                                                                                                                                      | IUGR Scores M(SD) | Control Scores M(SD) | Strength of Effects                               |
|-------------------------------------|-------------|----------------------|------------------------------------------------------------------------------------------------|---------------------------------|-------------------------------|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------|---------------------------------------------------|
| Between Group Studies               |             |                      |                                                                                                |                                 |                               |                                          |                                                                                                                                                                                           |                   |                      |                                                   |
| Doppler Velocimetry                 |             |                      |                                                                                                |                                 |                               |                                          |                                                                                                                                                                                           |                   |                      |                                                   |
| Wienerroither et al., 2001          | **          | 23/23                | IUGR = AC <10 <sup>th</sup> percentile and AREFV in UA                                         | Dating <20, Doppler until birth | UA                            | 3- 8 yrs Audiogram                       | IUGR group performed worse than controls on audiogram left 2 Hz (p<.005) and left 8 Hz (p<.05).                                                                                           |                   |                      | SMD=1.43(0.52-2.35)                               |
| Schreuder et al., 2002              | **          | 9/27/40 <sup>μ</sup> | IUGR = REDFV                                                                                   | Last assessment before delivery | UA                            | 5-12 yrs Pure Tone Diagnostic Audiometer | No differences in auditory function between REDFV, AEDFV and FEDFV groups (p>.05). There were 0/6 in the REDFV 1/16 in the AREFV group and 2/26 in the FEDFV group with affected hearing, |                   |                      | SMD= -0.38(1.76-0.10)                             |
| Regression Analysis Preterm Studies |             |                      |                                                                                                |                                 |                               |                                          |                                                                                                                                                                                           |                   |                      |                                                   |
| Doppler Velocimetry                 |             |                      |                                                                                                |                                 |                               |                                          |                                                                                                                                                                                           |                   |                      |                                                   |
| Baschat et al., 2009                | *           | 72 <sup>^</sup>      | IUGR = AC < 5 <sup>th</sup> percentile and elevated UA-PI. Elevation of DV-PI>2 SD = abnormal. | UA, MCA, DV                     | Final measure before delivery | 2 yrs CAT/CLAM                           | UA-REDFV was associated with abnormal hearing outcome (p<.0001).                                                                                                                          |                   |                      | <b>UA-AREDFV and Hearing Outcome:</b><br>SMD=1.83 |

**Note.** β = ≈8 wks post birth ; ¥ = Abnormal MCA/Normal MCA/Controls; μ = REDFV/AEDFV/FEDFV; CAT/CLAM = Clinical Adaptive/Clinical Linguistic Auditory Milestone Age; \* = high risk of bias, \*\* = medium risk of bias, \*\*\* = low risk of bias

## Chapter 3

**Table S3.1. Small-for-gestational-age (SGA) 10<sup>th</sup> percentiles of birth weight (g) for gestational age by sex according to the United States National Reference for Fetal Growth<sup>1</sup>**

| Gestational age (weeks) | Male | Female |
|-------------------------|------|--------|
| 20                      | 270  | 256    |
| 21                      | 328  | 310    |
| 22                      | 388  | 368    |
| 23                      | 446  | 426    |
| 24                      | 504  | 480    |
| 25                      | 570  | 535    |
| 26                      | 644  | 592    |
| 27                      | 728  | 662    |
| 28                      | 828  | 760    |
| 29                      | 956  | 889    |
| 30                      | 1117 | 1047   |
| 31                      | 1308 | 1234   |
| 32                      | 1521 | 1447   |
| 33                      | 1751 | 1675   |
| 34                      | 1985 | 1901   |
| 35                      | 2205 | 2109   |
| 36                      | 2407 | 2300   |
| 37                      | 2596 | 2484   |
| 38                      | 2769 | 2657   |
| 39                      | 2908 | 2796   |
| 40                      | 2986 | 2872   |
| 41                      | 3007 | 2891   |
| 42                      | 2998 | 2884   |
| 43                      | 2977 | 2868   |
| 44                      | 2963 | 2853   |

**Table S3.2. Birth weight (g), birth length (cm) and head circumference (HC) 10<sup>th</sup> percentiles at birth by sex according to MGRS growth standards**

|                    | Male  | Female |
|--------------------|-------|--------|
| Birth weight       | 2800  | 2700   |
| Birth length       | 47.50 | 46.80  |
| Head circumference | 32.80 | 32.40  |

MGRS = Multicentre Growth Reference Study

<sup>1</sup>Alexander, G. R., Himes, J. H., Kaufman, R. B., Mor, J., & Kogan, M. (1996). A United States National Reference for Fetal Growth. *Obstetrics & Gynecology*, 87(2), 163-168.

**Table S3.3. Birth weight, birth length and head circumference 10<sup>th</sup> percentiles for gestational age and sex according to INTERGROWTH-21<sup>st</sup> growth standards**

| Gestational age<br>(weeks) | Birth weight (g) |        | Birth length (cm) |        | Head circumference (cm) |        |
|----------------------------|------------------|--------|-------------------|--------|-------------------------|--------|
|                            | Male             | Female | Male              | Female | Male                    | Female |
| 33                         | 1430             | 1410   | 41.09             | 41.01  | 29.11                   | 28.76  |
| 34                         | 1710             | 1680   | 42.38             | 42.22  | 29.76                   | 29.44  |
| 35                         | 1950             | 1920   | 43.54             | 43.30  | 30.37                   | 30.06  |
| 36                         | 2180             | 2140   | 44.58             | 44.26  | 30.93                   | 30.62  |
| 37                         | 2380             | 2330   | 45.52             | 45.11  | 31.46                   | 31.13  |
| 38                         | 2570             | 2500   | 46.37             | 45.88  | 31.95                   | 31.59  |
| 39                         | 2730             | 2650   | 47.13             | 46.56  | 32.42                   | 32.01  |
| 40                         | 2880             | 2780   | 47.83             | 47.17  | 32.86                   | 32.39  |
| 41                         | 3010             | 2890   | 48.46             | 47.72  | 33.26                   | 32.74  |
| 42                         | 3120             | 2980   | 49.04             | 48.21  | 33.68                   | 33.06  |



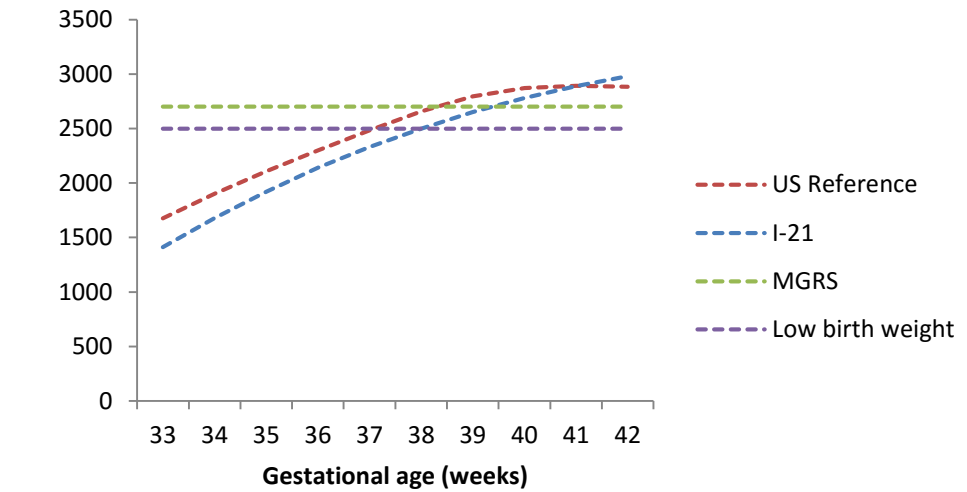
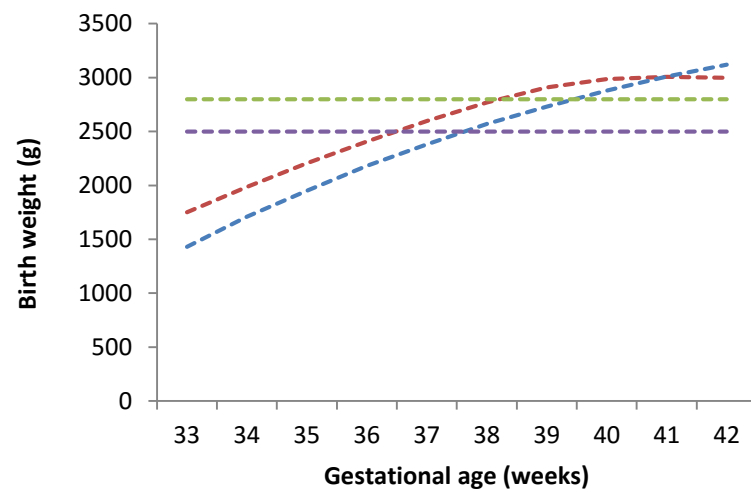
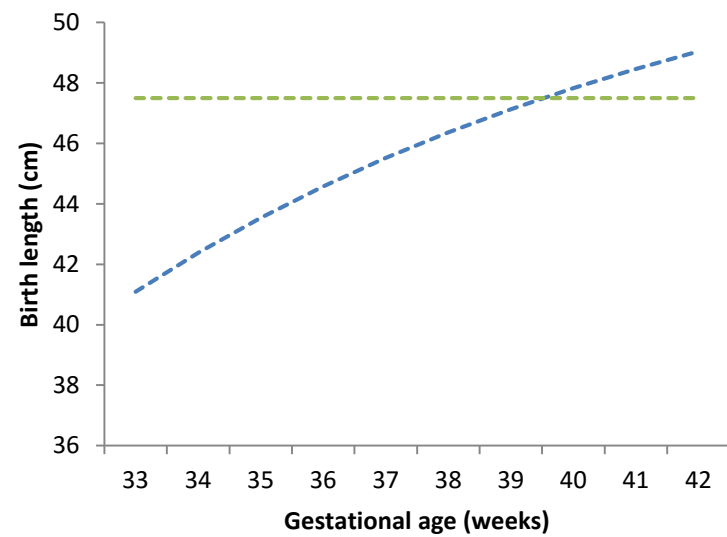
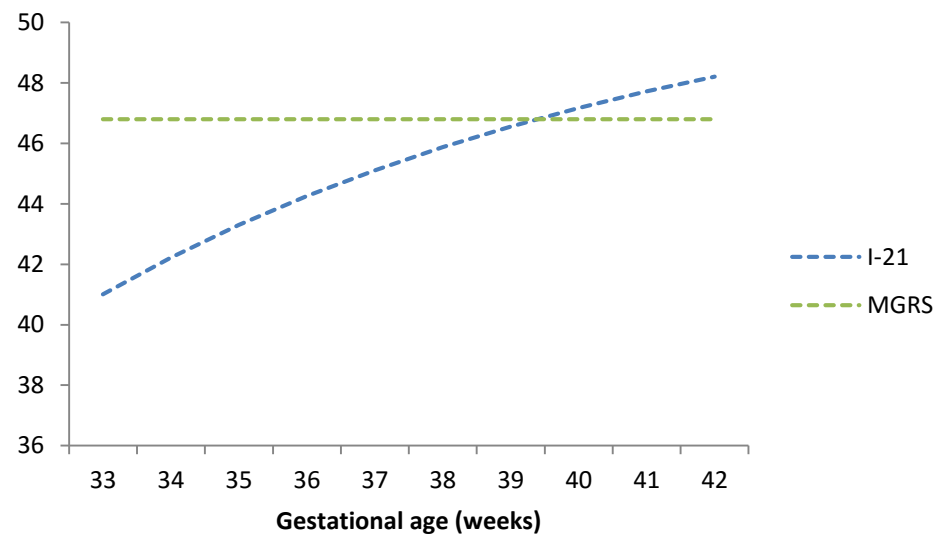


Figure S3.1. Birth weight-for-gestational-age for (A) males and (B) females according to the United States National Reference for Fetal Growth, the MGRS growth standards and the INTERGROWTH-21<sup>st</sup> growth standards. Mean area under the curve (AUC): US Reference = 24.87kg\*weeks; MGRS = 27.50kg\*weeks; INTERGROWTH-21<sup>st</sup> = 22.81kg\*weeks; Low birth weight = 25.00kg\*weeks.

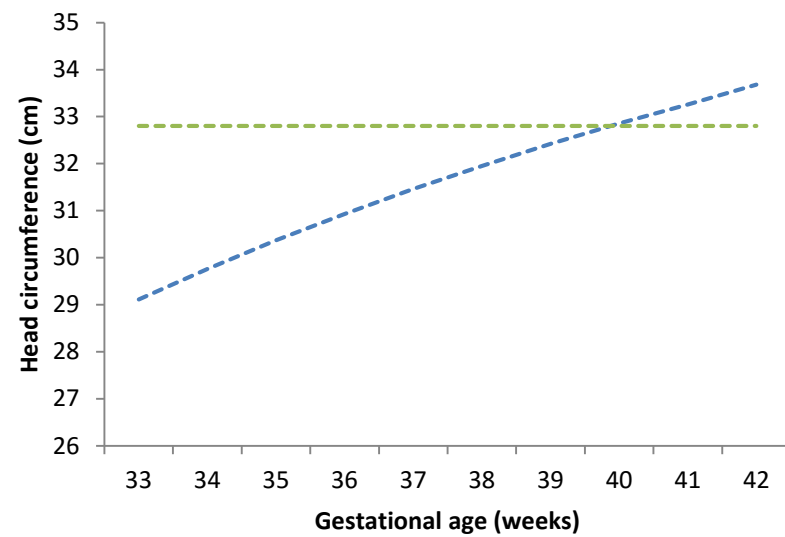


**A**

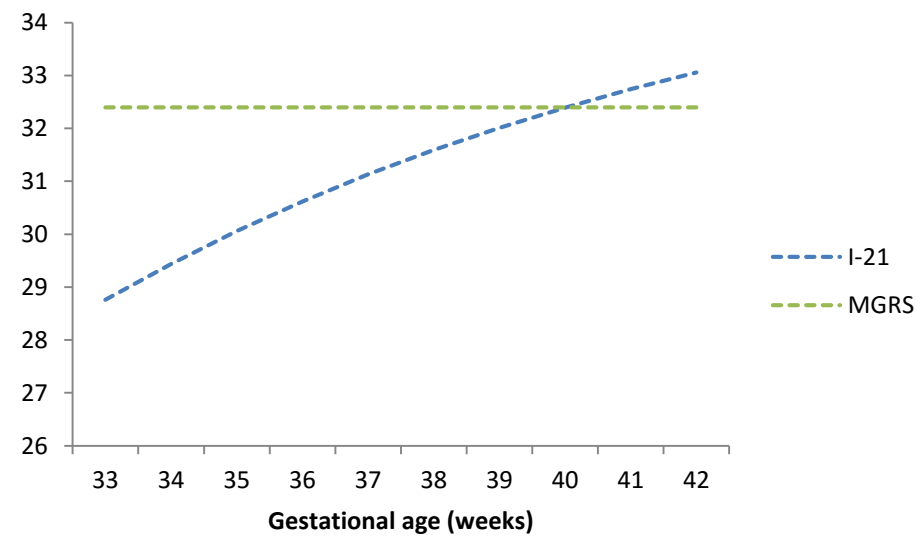


**B**

Figure S3.2. Birth length-for-gestational-age for (A) males and (B) females according to the MGRS growth standards and the INTERGROWTH-21<sup>st</sup> growth standards. Mean area under the curve (AUC): MGRS = 4.72m\*weeks; INTERGROWTH-21<sup>st</sup> = 4.50m\*weeks



**A**



**B**

**Figure S3.3.** Head circumference-for-gestational-age for (A) males and (B) females according to the MGRS growth standards and the INTERGROWTH-21<sup>st</sup> growth standards. Mean area under the curve (AUC): MGRS = 3.26m\*weeks; INTERGROWTH-21<sup>st</sup> = 3.12m\*weeks.

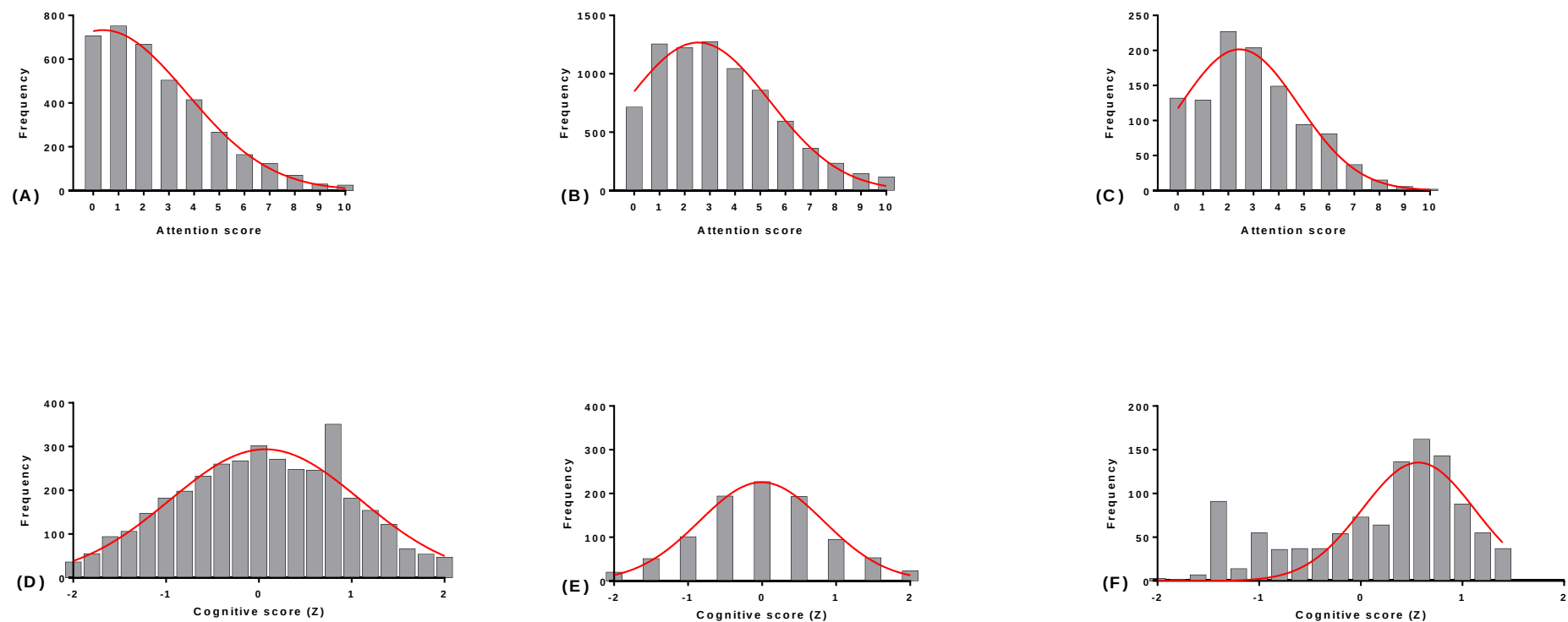


**Figure S3.4. Histograms of the frequency distribution of attention scores in (A) Pelotas, (B) ALSPAC and (C) INTERGROWTH-21st, and cognitive scores in (D) Pelotas, (E) ALSPAC, and (F) INTERGROWTH-21st, with Gaussian distribution curves plotted**

## Chapter 4

**Table S4.1. Cognitive domain corresponding items across the INTER-NDA, BSID-III and RND**

| Item                        | INTER-NDA |      | BSID-III  |      |       | RND       |      |                |
|-----------------------------|-----------|------|-----------|------|-------|-----------|------|----------------|
|                             | Domain    | Item | Domain    | Item | Level | Domain    | Item | Level          |
| Builds tower of 5 cubes     | Cognitive | 1    | Cognitive | 54   | M     | Cognitive | 8.2  | 24 mths        |
| 3 cubes of same colour      | Cognitive | 2    | Cognitive | 68   | Q     | Cognitive | 11.2 | 36 to <42 mths |
| Hands one cube              | Cognitive | 4    | Cognitive | 70   | Q     | -         | -    | -              |
| Puts spoon in cup           | Cognitive | 5    | RL        | 32   | Q     | Cognitive | 8.1  | 24 mths        |
| Shapes on board             | Cognitive | 6    | Cognitive | 56   | N     | Cognitive | 8.3  | 24 mths        |
| Shapes on rotated board     | Cognitive | 7    | Cognitive | 60   | O     | -         | -    | -              |
| Identifies 'door'           | Cognitive | 8    | RL        | 16   | M     | Cognitive | 7.4  | 18 to <24 mths |
| Looks towards object        | Cognitive | 11   | Cognitive | 32   | I     | Cognitive | 7.3  | 18 to <24 mths |
| Pretends to drink (self)    | Cognitive | 12   | Cognitive | 48   | M     | Cognitive | 7.2  | 18 to <24 mths |
| Makes cup of tea            | Cognitive | 13   | Cognitive | 71   | Q     | Cognitive | 9.7  | 25 to <30 mths |
| Gives doll drink            | Cognitive | 14   | Cognitive | 53   | M     | Cognitive | 7.6  | 18 to <24 mths |
| Identifies glitter bracelet | Cognitive | 16   | Cognitive | 50   | M     | -         | -    | -              |

RL=Receptive Language; mths = months

**Table S4.2. Expressive language domain corresponding items across the INTER-NDA, BSID-III and RNDA**

| Item                             | INTER-NDA |      | BSID-III |      |       | RNDA   |      |                |
|----------------------------------|-----------|------|----------|------|-------|--------|------|----------------|
|                                  | Domain    | Item | Domain   | Item | Level | Domain | Item | Level          |
| Names 4 colours                  | EL        | 3    | EL       | 41   | Q     | -      | -    | -              |
| Correct use of plurals           | EL        | 17   | EL       | 38   | Q     | -      | -    | -              |
| 2-4 syllable babble              | EL        | 23   | EL       | 13   | J     | -      | -    | -              |
| Uses 2 words together            | EL        | 24   | EL       | 18   | L     | Speech | 8.1  | 24 mths        |
| Indicates 'no' by word/gesture   | EL        | 25   | EL       | 24   | O     | -      | -    | -              |
| Use of pronoun                   | EL        | 26   | EL       | 30   | Q     | -      | -    | -              |
| Uses >=8 words                   | EL        | 27   | EL       | 23   | O     | -      | -    | -              |
| Uses 3 word sentences            | EL        | 28   | EL       | 29   | P     | Speech | 11.1 | 36 to <42 mths |
| Follows on topic of conversation | EL        | 29   | EL       | 33   | Q     | -      | -    | -              |
| Combines word and gesture        | EL        | 30   | EL       | 21   | N     | -      | -    | -              |

EL=Expressive Language; mths = months

**Table S4.3. Receptive language domain corresponding items across the INTER-NDA, BSID-III and RNDA**

| Item              | INTER-NDA |          | BSID-III |          |       |
|-------------------|-----------|----------|----------|----------|-------|
|                   | Domain    | Item no. | Domain   | Item no. | Level |
| Puts spoon in cup | Cognitive | 5        | RL       | 32       | Q     |
| Identifies 'door' | Cognitive | 8        | RL       | 16       | M     |

RL=Receptive Language

**Table S4.4. Behaviour domain corresponding items across the INTER-NDA, BSID-III and RNDA**

| Item               | INTER-NDA     |      | BSID-III  |      |       | RNDA      |      |                |
|--------------------|---------------|------|-----------|------|-------|-----------|------|----------------|
|                    | Domain        | Item | Domain    | Item | Level | Domain    | Item | Level          |
| Positive affect    | Behaviour (P) | 1    | Behaviour | 1    | -     | Behaviour | 2.3  | 18 to <24 mths |
| Exploration        | Behaviour (P) | 2    | Behaviour | 3    | -     | -         | -    | -              |
| Ease of engagement | Behaviour (P) | 3    | Behaviour | 4    | -     | -         | -    | -              |
| Cooperativeness    | Behaviour (P) | 4    | Behaviour | 5    | -     | Behaviour | 8.1  | 24 mths        |
| Adaptability       | Behaviour (P) | 5    | Behaviour | 7    | -     | -         | -    | -              |
| Distractibility    | Behaviour (N) | 6    | Behaviour | 9    | -     | -         | -    | -              |
| Negative affect    | Behaviour (N) | 7    | Behaviour | 13   | -     | -         | -    | -              |

P=Positive behaviour; N=Negative behaviour; mths = months

**Table S4.5. Scoring calculation for item 18 on INTER-NDA (maximum score)**

| BSID-III item | BSID-III level | INTER-NDA item | INTER-NDA score | Item 18 score    |
|---------------|----------------|----------------|-----------------|------------------|
| 68            | Q              | 3              | 4               | 3 (Occasionally) |
| 70            | Q              | 4              | 4               |                  |
| 71            | Q              | 13             | 4               |                  |

$\therefore \text{IF } \Sigma(3, 4, 13) = 12, \text{ THEN item 18} = 3$

**Table S4.6. Scoring calculation for item 18 on INTER-NDA (minimum score)**

| BSID-III item | BSID-III level | INTER-NDA item | INTER-NDA score | Item 18 score |
|---------------|----------------|----------------|-----------------|---------------|
| 68            | Q              | 3              | <4              | 1 (Never)     |
| 70            | Q              | 4              | <4              |               |
| 71            | Q              | 13             | <4              |               |

$\therefore \text{IF } \Sigma(3, 4, 13) < 12, \text{ THEN item 18} = 1$

**Table S4.7. Bias and limits of agreement values converted into BSID-III composite score equivalents of low, average and high INTER-NDA scores**

| Subscale            | Bias (limits of agreement) | Low INTER-NDA Score (Z=-2.0) | Mean INTER-NDA Score (Z=0.0) | High INTER-NDA Score (Z=+2.0) |
|---------------------|----------------------------|------------------------------|------------------------------|-------------------------------|
| Cognitive (total)   | .03 (-1.23 – 1.29)         | 70 (52-89)                   | 100 (82-119)                 | 130 (112-149)                 |
| Cognitive (mean)    | .05 (-1.02 – 1.13)         | 71 (55-88)                   | 101 (85-118)                 | 131 (115-148)                 |
| Receptive language  | .00 (-1.40 – 1.40)         | 70 (49-91)                   | 100 (79-121)                 | 130 (109-151)                 |
| Expressive language | .00 (-0.96 – 0.96)         | 70 (56-84)                   | 100 (86-114)                 | 130 (116-144)                 |
| Overall language    | .06 (-0.89 – 1.01)         | 71 (57-85)                   | 101 (87-115)                 | 131 (117-145)                 |
| Positive behaviour  | -.01 (-1.13 – 1.11)        | 70 (53-87)                   | 100 (83-117)                 | 130 (113-147)                 |
| Negative behaviour  | .00 (-1.34 – 1.34)         | 70 (50-90)                   | 100 (80-120)                 | 130 (110-150)                 |
| Overall behaviour   | -.05 (-1.03 – 0.93 )       | 69 (54-84)                   | 99 (84-114)                  | 129 (114-144)                 |



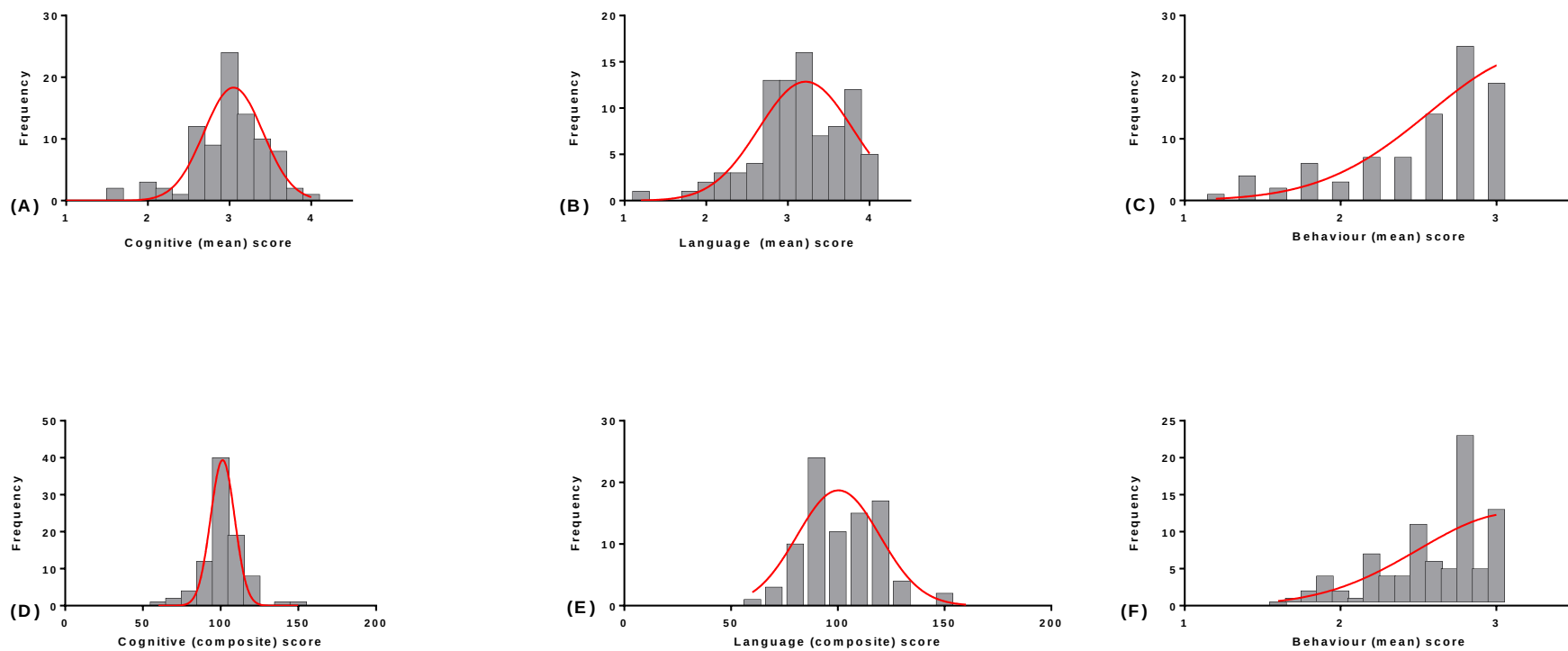


**Figure S3.4. Histograms of the frequency distribution of the INTER-NDA (A) cognitive, (B) language and (C) behaviour scores, and the BSID-III (D) cognitive, (E) language, and (F) behaviour scores, with Gaussian distribution curves plotted**

## Chapter 5

**Table S5.1. Descriptive statistics (*M*, *SD*), frequencies (*n*, %), ANOVA and chi-squared analyses comparing sample and loss-to-follow up in Pelotas**

| Variables                        | Sample (N=3749) | Loss (N=482) | F/ $\chi^2$ | <i>p</i> |
|----------------------------------|-----------------|--------------|-------------|----------|
| Birth weight (g)                 | 3171 (531)      | 2978 (769)   | 50.18       | <.001**  |
| Birth length (cm)                | 48.21 (2.51)    | 47.94 (3.12) | 4.30        | .038*    |
| Head circumference (cm)          | 34.00 (1.63)    | 33.85 (1.89) | 2.95        | .086     |
| Ponderal index                   | 2.81 (0.29)     | 2.82 (0.47)  | 0.32        | .575     |
| Body mass index                  | 13.56 (1.46)    | 13.48 (1.60) | 1.08        | .299     |
| Maternal school (years)          | 8.13 (3.45)     | 7.79 (3.66)  | 4.10        | .043*    |
| Maternal age at delivery (years) | 26.19 (6.84)    | 25.16 (6.56) | 9.86        | .002*    |
| Smoked during pregnancy          | 1018 (27.2%)    | 144 (29.9%)  | 1.58        | .213     |
| Preterm delivery (<37 weeks)     | 515 (13.8%)     | 98 (20.8%)   | 16.59       | <.001**  |
| Cesarean section                 | 1702 (45.4%)    | 220 (45.6%)  | 0.01        | .923     |
| Child sex (male)                 | 1943 (51.8%)    | 253 (52.5%)  | 0.08        | .809     |
| Low APGAR (<7)                   | 61 (1.6%)       | 31 (6.5%)    | 47.26       | <.001**  |

\* =  $p < .05$ ; \*\* =  $p < .001$

**Table S5.2. Descriptive statistics (M, SD), frequencies (n, %), ANOVA and chi-squared analyses comparing sample and loss-to-follow-up in ALSPAC**

| Variables                        | Sample (N=7829) | Loss (N=5788) | F/ $\chi^2$ | p       |
|----------------------------------|-----------------|---------------|-------------|---------|
| Birth weight (g)                 | 3443 (527)      | 3375 (557)    | 50.83       | <.001** |
| Birth length (cm)                | 50.76 (2.39)    | 50.54 (2.48)  | 21.03       | <.001** |
| Head circumference (cm)          | 34.83 (1.49)    | 34.75 (1.52)  | 6.45        | .011*   |
| Ponderal index                   | 2.62 (0.29)     | 2.64 (0.38)   | 1.85        | .174    |
| Body mass index                  | 13.32 (1.37)    | 13.30 (1.55)  | 0.88        | .349    |
| Maternal school (years)          | 11.07 (2.01)    | 10.33 (1.73)  | 419.49      | <.001** |
| Maternal age at delivery (years) | 28.94 (4.60)    | 26.64 (5.17)  | 745.40      | <.001** |
| Smoked during pregnancy          | 1556 (20.3%)    | 1658 (32.8%)  | 251.42      | <.001** |
| Preterm delivery (<37 weeks)     | 347 (4.4%)      | 339 (5.9%)    | 14.11       | <.001** |
| Cesarean section                 | 747 (9.9%)      | 408 (10.3%)   | 0.36        | .558    |
| Child sex (male)                 | 4020 (51.4%)    | 3003 (51.9%)  | 0.37        | .544    |
| Low APGAR (<7)                   | 45 (1.0%)       | 67 (2.1%)     | 16.45       | <.001** |

\* = p&lt;.05; \*\*=p&lt;.001

**Table S5.3. Descriptive statistics (M, SD), frequencies (n, %), ANOVA and chi-squared analyses comparing sample and loss-to-follow-up in INTERGROWTH-21st**

| Variables                        | Sample (N=1066) | Loss (N=1737) | F/ $\chi^2$ | p       |
|----------------------------------|-----------------|---------------|-------------|---------|
| Birth weight^ (g)                | 3228 (448)      | 3260 (420)    | 3.64        | .056    |
| Birth length^ (cm)               | 49.23 (1.83)    | 49.24 (1.78)  | 0.04        | .834    |
| Head circumference^ (cm)         | 34.05 (1.26)    | 34.04 (1.20)  | 0.02        | .886    |
| Maternal school (years)          | 15.31 (2.70)    | 14.94 (2.60)  | 12.99       | <.001** |
| Maternal age at delivery (years) | 28.82 (2.70)    | 28.74 (3.82)  | 0.36        | .549    |
| Preterm delivery (<37 weeks)     | 46 (4.3%)       | 98 (5.6%)     | 2.40        | .122    |
| Cesarean section                 | 424 (39.7%)     | 634 (36.5%)   | 2.98        | .085    |
| Child sex (male)                 | 526 (49.3%)     | 841 (48.4%)   | 0.21        | .644    |

^ data including only those born &gt;37 weeks gestational age for comparison; \* = p&lt;.05; \*\*=p&lt;.001

**Table S5.4. Bivariate correlations (r) between birth indices and attention and cognitive outcomes in Pelotas**

| Variables | BW     | BL     | HC     | PI     | BMI    | HC/BL  | HC/PI  | HC/BMI | Attention | Cognition |
|-----------|--------|--------|--------|--------|--------|--------|--------|--------|-----------|-----------|
| BW        | -      | .82**  | .77**  | .48**  | .84**  | -.16** | -.14** | -.66** | -.10**    | .14**     |
| BL        | .82**  | -      | .69**  | -.08** | .40**  | -.49** | .41**  | -.19** | -.09**    | .14**     |
| HC        | .77**  | .69**  | -      | .35**  | .64**  | .27**  | .13**  | -.30** | -.09**    | .16**     |
| PI        | .48**  | -.08** | .35**  | -      | .88**  | .49**  | -.86** | -.88** | -.04*     | .06**     |
| BMI       | .84**  | .40**  | .64**  | .88**  | -      | .21**  | -.61** | -.91** | -.08**    | .12*      |
| HC/BL     | -.16** | -.49** | .27**  | .49**  | .21**  | -      | -.38** | -.10** | .02       | .00       |
| HC/PI     | -.14** | .41**  | .13**  | -.86** | -.61** | -.38** | -      | .82**  | .01       | .01       |
| HC/BMI    | -.66** | -.19** | -.30** | -.88** | -.91** | -.10** | .82**  | -      | .06**     | -.08**    |
| Attention | -.10** | -.09** | -.09** | -.04*  | -.08** | .02    | .01    | .06**  | -         | -.29**    |
| Cognition | .14**  | .14**  | .16**  | .06**  | .12**  | .00    | .01    | -.08** | -.29**    | -         |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S5.5. Bivariate correlations (r) between birth indices and attention and cognitive outcomes in ALSPAC**

| Variables | BW     | BL     | HC     | PI     | BMI    | HC/BL  | HC/PI  | HC/BMI | Attention | Cognition |
|-----------|--------|--------|--------|--------|--------|--------|--------|--------|-----------|-----------|
| BW        | -      | .74**  | .71**  | .37**  | .75**  | -.12** | -.18** | -.60** | -.06**    | .05       |
| BL        | .74**  | -      | .53**  | -.30** | .13**  | -.56** | .48**  | .01    | -.04**    | .05       |
| HC        | .71**  | .53**  | -      | .32**  | .56**  | .39**  | .08**  | -.20** | -.05**    | .05       |
| PI        | .37**  | -.30** | .32**  | -      | .89**  | .67**  | -.84** | -.82** | -.02      | .00       |
| BMI       | .75**  | .13**  | .56**  | .89**  | -      | .40**  | -.71** | -.89** | -.04**    | .02       |
| HC/BL     | -.12** | -.56** | .39**  | .67**  | .40**  | -      | -.42** | -.20** | .01       | -.01      |
| HC/PI     | -.18** | .48**  | .08**  | -.84** | -.71** | -.42** | -      | .88**  | .00       | .02       |
| HC/BMI    | -.60** | .01    | -.20** | -.82** | -.89** | -.20** | .88**  | -      | .03**     | .00       |
| Attention | -.06** | -.04** | -.05** | -.02   | -.04** | .01    | .00    | .03**  | -         | -.29**    |
| Cognition | .05    | .05    | .05    | .00    | .02    | -.01   | .02    | .00    | -.29**    | -         |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S5.6. Bivariate correlations (*r*) between birth indices and attention and cognitive outcomes in INTERGROWTH-21st**

| Variables | BW     | BL     | HC     | PI     | BMI    | HC/BL  | HC/PI  | HC/BMI | Attention | Cognition |
|-----------|--------|--------|--------|--------|--------|--------|--------|--------|-----------|-----------|
| BW        | -      | .78**  | .78**  | .60**  | .87**  | -.04   | -.31** | -.70** | -.05      | -.01      |
| BL        | .78**  | -      | .68**  | -.02   | .38**  | -.44** | .32**  | -.16** | -.03      | -.03      |
| HC        | .78**  | .68**  | -      | .39**  | .63**  | .36**  | .02    | -.32** | -.07*     | .01       |
| PI        | .60**  | -.02   | .39**  | -      | .91**  | .51**  | -.90** | -.93** | -.04      | .03       |
| BMI       | .87**  | .38**  | .63**  | .91**  | -      | .29**  | -.71** | -.92** | -.05      | .01       |
| HC/BL     | -.04   | -.44*  | .36**  | .51**  | .29**  | -      | -.38** | -.19** | -.04      | .05       |
| HC/PI     | -.31** | .32**  | .02    | -.90** | -.71** | -.38** | -      | .89**  | .02       | -.03      |
| HC/BMI    | -.70** | -.16** | -.32** | -.93** | -.92** | -.19** | .89**  | -      | .03       | -.02      |
| Attention | -.05   | -.03   | -.07   | -.04** | -.05   | -.04   | .02    | .03    | -         | -.35**    |
| Cognition | -.01   | -.03   | .01    | .03    | .01    | .05    | -.03   | -.02   | -.35**    | -         |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; PI=ponderal index; SGA=small-for-gestational-age; \* =  $p < .05$ ; \*\*= $p < .001$

**Table S5.7. Descriptives (*M, SD*) of attention and cognitive outcome scores by birth exposures in Pelotas**

| Variable (N)                             | Attention   | Cognition     |
|------------------------------------------|-------------|---------------|
| Birth weight indices                     |             |               |
| BW <2500g                                | 3.09 (2.72) | 94.17 (17.50) |
| SGA                                      | 3.02 (2.67) | 95.76 (16.54) |
| BW <10 <sup>th</sup> MGRS                | 2.98 (2.53) | 95.32 (16.77) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 3.24 (2.82) | 94.69 (16.63) |
| Stunting indices                         |             |               |
| BL < 10 <sup>th</sup> MGRS               | 2.50 (2.25) | 96.61 (17.03) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.99 (2.56) | 96.36 (16.70) |
| HC <10 <sup>th</sup> MGRS                | 3.10 (2.53) | 93.82 (17.09) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 3.08 (2.56) | 92.58 (16.58) |
| Wasting indices                          |             |               |
| PI <10 <sup>th</sup> percentile          | 2.93 (2.57) | 95.37 (16.08) |
| PI-for-age <10 <sup>th</sup> percentile  | 2.76 (2.51) | 97.63 (16.45) |
| BMI <10 <sup>th</sup> percentile         | 3.10 (2.72) | 93.79 (17.35) |
| BMI-for-age <10 <sup>th</sup> percentile | 2.93 (2.54) | 96.71 (16.42) |
| Asymmetry indices                        |             |               |
| HC/BL >90 <sup>th</sup> percentile       | 2.89 (2.39) | 97.32 (17.06) |
| HC/PI >90 <sup>th</sup> percentile       | 2.88 (2.50) | 95.63 (17.23) |
| HC/BMI >90 <sup>th</sup> percentile      | 2.88 (2.50) | 95.64 (17.23) |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

**Table S5.8. Descriptives (*M, SD*) of attention and cognitive outcome scores by birth exposures in ALSPAC**

| Variable (N)                             | Attention   | Cognition      |
|------------------------------------------|-------------|----------------|
| Birth weight indices                     |             |                |
| BW <2500g                                | 3.63 (2.62) | 102.50 (11.80) |
| SGA                                      | 3.51 (2.73) | 102.54 (12.56) |
| BW <10 <sup>th</sup> MGRS                | 3.84 (2.50) | 101.70 (11.90) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 3.61 (2.73) | 102.13 (12.49) |
| Stunting indices                         |             |                |
| BL < 10 <sup>th</sup> MGRS               | 3.89 (2.58) | 100.51 (12.57) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 4.04 (2.57) | 98.74 (13.08)  |
| HC <10 <sup>th</sup> MGRS                | 3.75 (2.82) | 100.38 (13.92) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 3.49 (2.74) | 98.29 (12.96)  |
| Wasting indices                          |             |                |
| PI <10 <sup>th</sup> percentile          | 3.52 (2.38) | 103.61 (14.42) |
| PI-for-age <10 <sup>th</sup> percentile  | 3.43 (2.34) | 104.13 (14.69) |
| BMI <10 <sup>th</sup> percentile         | 3.60 (2.41) | 104.08 (12.65) |
| BMI-for-age <10 <sup>th</sup> percentile | 3.62 (2.48) | 104.26 (15.24) |
| Asymmetry indices                        |             |                |
| HC/BL >90 <sup>th</sup> percentile       | 3.52 (2.38) | 105.05 (14.81) |
| HC/PI >90 <sup>th</sup> percentile       | 3.34 (2.29) | 103.82 (13.74) |
| HC/BMI >90 <sup>th</sup> percentile      | 3.56 (2.42) | 103.54 (14.40) |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age



**Table S5.9. Descriptives (*M, SD*) of attention and cognitive outcome scores by birth exposures in INTERGROWTH-21st**

| Variable (N)                             | Attention   | Cognition    |
|------------------------------------------|-------------|--------------|
| Birth weight indices                     |             |              |
| BW <2500g                                | 2.90 (2.15) | 0.03 (1.18)  |
| SGA                                      | 2.99 (2.09) | 0.00 (1.04)  |
| BW <10 <sup>th</sup> MGRS                | 3.19 (2.23) | 0.02 (1.02)  |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.99 (2.16) | -0.10 (1.07) |
| Stunting indices                         |             |              |
| BL < 10 <sup>th</sup> MGRS               | 3.07 (2.22) | 0.15 (0.99)  |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 3.23 (2.36) | -0.03 (1.04) |
| HC <10 <sup>th</sup> MGRS                | 3.23 (2.18) | -0.04 (1.09) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 3.16 (2.30) | -0.08 (1.03) |
| Wasting indices                          |             |              |
| PI <10 <sup>th</sup> percentile          | 3.18 (2.18) | -0.21 (1.13) |
| PI-for-age <10 <sup>th</sup> percentile  | 3.26 (2.14) | -0.20 (1.06) |
| BMI <10 <sup>th</sup> percentile         | 3.24 (2.07) | 0.26 (1.13)  |
| BMI-for-age <10 <sup>th</sup> percentile | 3.16 (2.10) | -0.17 (1.04) |
| Asymmetry indices                        |             |              |
| HC/BL >90 <sup>th</sup> percentile       | 2.87 (2.21) | 0.04 (1.05)  |
| HC/PI >90 <sup>th</sup> percentile       | 3.03 (2.23) | -0.15 (1.05) |
| HC/BMI >90 <sup>th</sup> percentile      | 3.01 (2.21) | -0.11 (1.10) |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age

**Table S5.10. Description of Pelotas maternal characteristics, and ordinal odds of higher attention problem score (CBCL) and lower cognitive score (WPPSI)**

| Variable (N)                                           | n (%)       | Attention         |         | Cognition         |         |
|--------------------------------------------------------|-------------|-------------------|---------|-------------------|---------|
|                                                        |             | OR (95%CI)        | p       | OR (95%CI)        | p       |
| <b>Family income quintiles (3733)</b>                  |             |                   | <.001** |                   | <.001** |
| 1                                                      | 872 (23.4)  | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| 2                                                      | 785 (21.0)  | 0.96 (0.81-1.15)  |         | 0.78 (0.64-0.96)  |         |
| 3                                                      | 836 (22.4)  | 0.71 (0.60-0.85)  |         | 0.53 (0.43-0.66)  |         |
| 4                                                      | 593 (15.9)  | 0.54 (0.45-0.64)  |         | 0.33 (0.26-0.40)  |         |
| 5                                                      | 647 (17.3)  | 0.38 (0.31-0.45)  |         | 0.18 (0.14-0.22)  |         |
| <b>Maternal schooling (years) (3712)</b>               |             |                   | <.001** |                   | <.001** |
| <9                                                     | 2109 (56.8) | 1.82 (1.60-2.02)  |         | 4.03 (3.48-4.67)  |         |
| ≥9                                                     | 1603 (43.2) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Maternal age (years) (3747)</b>                     |             |                   | <.001** |                   | <.001** |
| ≤19                                                    | 702 (18.7)  | 1.53 (1.32-1.77)  |         | 1.57 (1.32-1.85)  |         |
| 20-34                                                  | 2530 (67.5) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| ≥35                                                    | 515 (13.7)  | 0.79 (0.67-0.93)  |         | 0.89 (0.73-1.08)  |         |
| <b>Maternal BMI (2195)</b>                             |             |                   | .493    |                   | .068    |
| <18.5                                                  | 82 (3.7)    | 1.26 (0.85-1.87)  |         | 0.97 (0.59-1.59)  |         |
| 18.5-29.9                                              | 1840 (83.8) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| ≥30.0                                                  | 273 (12.4)  | 0.97 (0.77-1.22)  |         | 0.76 (0.59-0.98)  |         |
| <b>Maternal skin colour (3749)</b>                     |             |                   | <.001** |                   | <.001** |
| Black                                                  | 755 (20.1)  | 1.52 (1.32-1.76)  |         | 2.57 (2.18-3.03)  |         |
| Other                                                  | 254 (6.8)   | 1.54 (1.23-1.92)  |         | 1.60 (1.23-2.08)  |         |
| White                                                  | 2740 (73.1) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Parity (3748)</b>                                   |             |                   | .040*   |                   | <.001** |
| ≥2                                                     | 1276 (34.0) | 1.07 (0.94-1.23)  |         | 1.77 (1.52-2.06)  |         |
| 1                                                      | 997 (26.6)  | 0.89 (0.77-1.02)  |         | 1.13 (0.96-1.33)  |         |
| 0                                                      | 1475 (39.4) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Smoked during pregnancy (3749)</b>                  |             |                   | <.001** |                   | <.001** |
| Yes                                                    | 1018 (27.2) | 1.92 (1.69-2.18)  |         | 1.65 (1.42-1.90)  |         |
| No                                                     | 2731 (72.8) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Consumed alcohol during pregnancy (3749)</b>        |             |                   | .003*   |                   | .467    |
| Yes                                                    | 125 (3.3)   | 1.59 (1.69-2.18)  |         | 1.14 (0.80-1.63)  |         |
| No                                                     | 3624 (96.7) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Maternal mental illness during pregnancy (3747)</b> |             |                   | <.001** |                   | <.001** |
| Yes                                                    | 916 (24.4)  | 1.83 (1.60-2.09)  |         | 1.43 (1.23-1.67)  |         |
| No                                                     | 2831 (75.6) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>High blood pressure during pregnancy (3742)</b>     |             |                   | .043*   |                   | <.001** |
| Yes                                                    | 899 (24.0)  | 1.15 (1.00-1.31)  |         | 1.39 (1.20-1.62)  |         |
| No                                                     | 2843 (76.0) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Diabetes during pregnancy (3746)</b>                |             |                   | .243    |                   | .438    |
| Yes                                                    | 115 (3.1)   | 1.21(0.88-1.68)   |         | 0.86 (0.59-1.23)  |         |
| No                                                     | 3631 (96.9) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |

**Table S5.11. Description of Pelotas child characteristics, and ordinal odds of higher attention problem score (CBCL) and lower cognitive score (WPPSI-R)**

| Variable (N)                                           | n (%)       | Attention          |         | Cognition           |         |
|--------------------------------------------------------|-------------|--------------------|---------|---------------------|---------|
|                                                        |             | OR (95% CI)        | p       | OR (95%CI)          | p       |
| <b>Sex of child (3749)</b>                             |             |                    | <.001** |                     | <.001** |
| Male                                                   | 1943 (51.8) | 1.43 (1.28-1.60)   |         | 1.47 (1.29-1.68)    |         |
| Female                                                 | 1806 (48.2) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>Gestational age at birth (3745)</b>                 |             |                    | <.001** |                     | <.001** |
| ≤28 weeks                                              | 6 (0.2)     | 11.01 (2.09-58.07) |         | 24.41 (2.86-208.54) |         |
| 28-32 weeks                                            | 37 (1.0)    | 1.44 (0.84-2.49)   |         | 4.10 (2.18-7.74)    |         |
| 32-37 weeks                                            | 472 (12.6)  | 1.37 (1.15-1.62)   |         | 1.72 (1.41-2.09)    |         |
| ≥37 weeks                                              | 3230 (86.2) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>Birth weight (3748)</b>                             |             |                    | .002*   |                     | <.001** |
| <2500g                                                 | 340 (9.1)   | 1.38 (1.13-1.69)   |         | 2.11 (1.68-2.63)    |         |
| ≥2500g                                                 | 3408 (90.0) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>Mode of delivery (3749)</b>                         |             |                    | .041*   |                     | <.001** |
| Cesarean                                               | 1702 (45.4) | 0.89 (0.79-1.00)   |         | 0.64 (0.56-0.73)    |         |
| Normal                                                 | 2047 (54.6) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>Multiple birth (3749)</b>                           |             |                    | .421    |                     | <.001** |
| Twins                                                  | 76 (2.0)    | 1.17 (0.80-1.72)   |         | 2.67 (1.70-4.20)    |         |
| Single                                                 | 3673 (98.0) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>MGRS Head circumference (3735)</b>                  |             |                    | <.001** |                     | <.001** |
| <10 <sup>th</sup> percentile                           | 606 (16.2)  | 1.52 (1.31-1.78)   |         | 2.30 (1.98-2.75)    |         |
| ≥10 <sup>th</sup> percentile                           | 3129 (83.8) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>APGAR score at 1 min (3726)</b>                     |             |                    | .223    |                     | .084    |
| <7                                                     | 432 (11.6)  | 1.16 (0.94-1.33)   |         | 1.20 (0.98-1.47)    |         |
| ≥7                                                     | 3294 (88.4) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>APGAR score at 5 min (3730)</b>                     |             |                    | .004*   |                     | .002*   |
| <7                                                     | 61 (1.6)    | 1.94 (1.23-3.06)   |         | 2.19 (1.34-3.59)    |         |
| ≥7                                                     | 3669 (98.4) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>Duration of breastfeeding (3742)</b>                |             |                    | <.001** |                     | <.001** |
| No breastfeeding                                       | 100 (2.8)   | 2.00 (1.39-2.87)   |         | 3.37 (2.24-5.06)    |         |
| ≤6 months                                              | 1754 (46.8) | 1.12 (1.00-1.25)   |         | 1.39 (1.22-1.60)    |         |
| >6 months                                              | 1888 (50.4) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>Hospitalisation during first 3 months (3669)</b>    |             |                    | <.001** |                     | <.001** |
| Yes                                                    | 239 (6.5)   | 1.59 (1.25-2.01)   |         | 1.90 (1.46-2.47)    |         |
| No                                                     | 3430 (93.5) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>Presence of neurological illness (3749)</b>         |             |                    | <.001** |                     | <.001** |
| Yes                                                    | 53 (1.4)    | 2.90 (1.79-4.69)   |         | 3.48 (2.02-6.00)    |         |
| No                                                     | 3696 (98.6) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>Head circumference at 24 months (3668)</b>          |             |                    | .004*   |                     | <.001** |
| <10 <sup>th</sup> percentile                           | 374 (10.2)  | 1.32 (1.09-1.59)   |         | 2.41 (1.95-2.98)    |         |
| ≥10 <sup>th</sup> percentile                           | 3294 (89.8) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| <b>Height-for-age at 24 months (z score) (3661)</b>    |             |                    | <.001** |                     | <.001** |
| < -2.0                                                 | 176 (4.8)   | 1.71 (1.31-2.24)   |         | 4.33 (3.21-5.84)    |         |
| -2.0 – 2.0                                             | 3369 (92.0) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| >2.0                                                   | 116 (3.2)   | 0.72 (0.53-1.00)   |         | 0.54 (0.38-0.79)    |         |
| <b>Weight-for-height at 24 months (z score) (3661)</b> |             |                    | .273    |                     | <.001** |
| < -2.0                                                 | 28 (0.8)    | 1.24 (0.63-2.45)   |         | 5.12 (2.39-10.97)   |         |
| -2.0 – 2.0                                             | 3343 (91.3) | 1.00 <sup>a</sup>  |         | 1.00 <sup>a</sup>   |         |
| >2.0                                                   | 290 (7.9)   | 0.85 (0.69-1.06)   |         | 0.90 (0.71-1.15)    |         |

**Table S5.12. Description of ALSPAC maternal characteristics, and ordinal odds of higher attention problem score (SDQ) and lower cognitive score (WPPSI-R)**

| Variable (N)                                           | n (%)       | Attention         |         | Cognition         |         |
|--------------------------------------------------------|-------------|-------------------|---------|-------------------|---------|
|                                                        |             | OR (95%CI)        | p       | OR (95%CI)        | p       |
| <b>Family income (8012)</b>                            |             |                   | <.001** |                   | <.001** |
| <£100                                                  | 660 (8.2)   | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| £100-199                                               | 1366 (17.0) | 0.84 (0.70-1.01)  |         | 1.38 (0.77-2.48)  |         |
| £200-299                                               | 2298 (28.7) | 0.69 (0.58-0.82)  |         | 0.87 (0.50-1.50)  |         |
| £300-399                                               | 1729 (21.6) | 0.65 (0.54-0.78)  |         | 0.51 (0.29-0.89)  |         |
| ≥£400                                                  | 1959 (24.5) | 0.59 (0.49-0.70)  |         | 0.32 (0.19-0.55)  |         |
| <b>Maternal schooling (years) (9459)</b>               |             |                   | <.001** |                   | <.001** |
| <9                                                     | 2448 (25.9) | 1.24 (1.14-1.36)  |         | 3.44 (2.58-4.59)  |         |
| ≥9                                                     | 7011 (74.1) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Maternal age (years) (9795)</b>                     |             |                   | <.001** |                   | .002*   |
| ≤19                                                    | 290 (3.0)   | 1.82 (1.41-2.36)  |         | 3.14 (1.40-7.04)  |         |
| 20-34                                                  | 8436 (86.1) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| ≥35                                                    | 1069 (10.9) | 0.80 (0.71-0.90)  |         | 0.70 (0.49-1.00)  |         |
| <b>Maternal BMI (7166)</b>                             |             |                   | .233    |                   | <.001** |
| <18.5                                                  | 324 (4.5)   | 1.15 (0.94-1.40)  |         | 0.95 (0.54-1.70)  |         |
| 18.5-29.9                                              | 6473 (90.3) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| ≥30.0                                                  | 369 (5.1)   | 1.11 (0.94-1.40)  |         | 2.73 (1.70-4.40)  |         |
| <b>Maternal ethnicity (9426)</b>                       |             |                   | .059    |                   | .276    |
| Black                                                  | 72 (0.8)    | 1.07 (0.66-1.74)  |         | 1.61 (0.56-4.64)  |         |
| Other                                                  | 105 (1.1)   | 0.64 (0.44-0.93)  |         | 2.33 (0.68-7.96)  |         |
| White                                                  | 9249 (98.1) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Parity (9463)</b>                                   |             |                   | .003**  |                   | <.001** |
| ≥2                                                     | 1797 (19.0) | 0.83 (0.75-0.93)  |         | 2.17 (1.59-2.96)  |         |
| 1                                                      | 3333 (35.2) | 0.95 (0.87-1.03)  |         | 1.20 (0.92-1.56)  |         |
| 0                                                      | 4333 (45.8) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Smoked during pregnancy (9543)</b>                  |             |                   | <.001** |                   | .010*   |
| Yes                                                    | 2083 (21.8) | 1.51 (1.37-1.66)  |         | 1.47 (1.10-1.98)  |         |
| No                                                     | 7460 (78.2) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Consumed alcohol during pregnancy (9352)</b>        |             |                   | .201    |                   | .391    |
| Yes                                                    | 6080 (65.0) | 1.05 (0.97-1.14)  |         | 0.90 (0.70-1.15)  |         |
| No                                                     | 3272 (35.0) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Maternal mental illness during pregnancy (9235)</b> |             |                   | <.001** |                   | .023*   |
| Yes                                                    | 1266 (13.7) | 1.56 (1.39-1.75)  |         | 1.54 (1.06-2.22)  |         |
| No                                                     | 7926 (86.3) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>High blood pressure during pregnancy (7513)</b>     |             |                   | .229    |                   | .029*   |
| Yes                                                    | 1071 (14.3) | 1.07 (0.96-1.20)  |         | 1.43 (1.04-1.98)  |         |
| No                                                     | 6442 (85.7) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |
| <b>Diabetes during pregnancy (7618)</b>                |             |                   | .001*   |                   | .535    |
| Yes                                                    | 71 (0.9)    | 1.96 (1.29-2.96)  |         | 0.69 (0.22-2.22)  |         |
| No                                                     | 7547 (99.1) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup> |         |

**Table S5.13. Description of ALSPAC child characteristics, and ordinal odds of higher attention problem score (SDQ) and lower cognitive score (WPPSI-R)**

| Variable (N)                                          | n (%)       | Attention         |         | Cognition           |         |
|-------------------------------------------------------|-------------|-------------------|---------|---------------------|---------|
|                                                       |             | OR (95%CI)        | p       | OR (95%CI)          | p       |
| <b>Sex of child (9795)</b>                            |             |                   | <.001** |                     | .012*   |
| Male                                                  | 5067 (51.7) | 1.69 (1.57-1.82)  |         | 1.34 (1.07-1.68)    |         |
| Female                                                | 4728 (48.3) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup>   |         |
| <b>Gestational age at birth (9795)</b>                |             |                   | .021*   |                     | .116    |
| ≤28 weeks                                             | 23 (0.2)    | 1.36 (0.56-3.31)  |         | 16.49 (0.66-409.52) |         |
| 28-32 weeks                                           | 58 (0.6)    | 1.71 (1.05-2.80)  |         | 0.07 (0.00-1.51)    |         |
| 32-37 weeks                                           | 377 (3.8)   | 1.25 (1.02-1.52)  |         | 1.10 (0.63-1.95)    |         |
| ≥37 weeks                                             | 9337 (95.3) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup>   |         |
| <b>Birth weight (9678)</b>                            |             |                   | <.001** |                     | .689    |
| <2500g                                                | 363 (3.8)   | 1.49 (1.21-1.82)  |         | 1.14 (0.60-2.15)    |         |
| ≥2500g                                                | 9315 (96.2) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup>   |         |
| <b>Mode of delivery (9264)</b>                        |             |                   | .092    |                     | .116    |
| Cesarean                                              | 921 (9.9)   | 0.90 (0.79-1.02)  |         | 1.34 (0.93-1.93)    |         |
| Normal                                                | 8343 (90.1) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup>   |         |
| <b>MGRS head circumference (7699)</b>                 |             |                   | <.001** |                     | .214    |
| <10 <sup>th</sup> percentile                          | 386 (5.0)   | 1.59 (1.31-1.94)  |         | 1.43 (0.81-2.53)    |         |
| ≥10 <sup>th</sup> percentile                          | 7313 (95.0) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup>   |         |
| <b>APGAR score at 5 min (5848)</b>                    |             |                   | .029*   |                     | .441    |
| <7                                                    | 75 (1.3)    | 0.59 (0.36-0.95)  |         | 0.61 (0.17-2.17)    |         |
| ≥7                                                    | 5773 (98.7) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup>   |         |
| <b>Duration of breastfeeding (9142)</b>               |             |                   | <.001** |                     | <.001** |
| No breastfeeding                                      | 2245 (24.6) | 1.38 (1.24-1.53)  |         | 2.76 (1.98-3.84)    |         |
| ≤6 months                                             | 3645 (39.9) | 1.35 (1.24-1.48)  |         | 1.52 (1.16-1.98)    |         |
| >6 months                                             | 3252 (35.6) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup>   |         |
| <b>Neonatal admission to hospital (9407)</b>          |             |                   | <.001** |                     | .492    |
| Yes                                                   | 565 (6.0)   | 1.34 (1.14-1.58)  |         | 1.19 (0.73-1.94)    |         |
| No                                                    | 8842 (94.0) | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup>   |         |
| <b>Head circumference at 24 months (982)</b>          |             |                   | .955    |                     | <.001** |
| <10 <sup>th</sup> percentile                          | 100 (10.2)  | 1.01 (0.67-1.54)  |         | 2.11 (1.39-3.18)    |         |
| ≥10 <sup>th</sup> percentile                          | 882 (89.8)  | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup>   |         |
| <b>Height-for-age at 24 months (z score) (929)</b>    |             |                   | .002*   |                     | .777    |
| < -2.0                                                | 21 (2.3)    | 0.57 (0.20-1.59)  |         | 0.74 (0.32-1.70)    |         |
| -2.0 – 2.0                                            | 885 (95.3)  | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup>   |         |
| >2.0                                                  | 23 (2.5)    | 3.60 (1.68-7.74)  |         | 0.98 (0.43-2.26)    |         |
| <b>Weight-for-height at 24 months (z score) (928)</b> |             |                   | .039*   |                     | .923    |
| < -2.0                                                | 5 (0.5)     | 0.42 (0.09-1.92)  |         | 0.80 (0.20-3.21)    |         |
| -2.0 – 2.0                                            | 893 (96.1)  | 1.00 <sup>a</sup> |         | 1.00 <sup>a</sup>   |         |
| >2.0                                                  | 31 (3.3)    | 2.30 (1.13-4.68)  |         | 0.92 (0.48-1.78)    |         |

**Table S5.14. Description of INTERGROWTH-21st maternal and child characteristics, and ordinal odds of higher attention problem score (CBQ) and lower cognitive score (INTER-NDA)**

| Variable (N)                             | n (%)       | Attention         |       | Cognition         |       |
|------------------------------------------|-------------|-------------------|-------|-------------------|-------|
|                                          |             | OR (95%CI)        | p     | OR (95%CI)        | p     |
| <b>Maternal schooling (years) (1076)</b> |             |                   | .180  |                   | .814  |
| <9                                       | 39 (3.6)    | 0.68 (0.39-1.19)  |       | 0.93 (0.51-1.71)  |       |
| ≥9                                       | 1037 (96.4) | 1.00 <sup>a</sup> |       | 1.00 <sup>a</sup> |       |
| <b>Maternal age (years) (1076)</b>       |             |                   | .007* |                   | .952  |
| <25                                      | 236 (21.9)  | 1.32 (0.98-1.77)  |       | 1.02 (0.75-1.40)  |       |
| 25-30                                    | 351 (32.6)  | 1.00 <sup>a</sup> |       | 1.00 <sup>a</sup> |       |
| ≥30                                      | 489 (45.4)  | 0.85 (0.67-1.08)  |       | 0.98 (0.76-1.26)  |       |
| <b>Maternal BMI (1076)</b>               |             |                   | .927  |                   | .505  |
| <25                                      | 775 (72.0)  | 1.00 <sup>a</sup> |       | 1.00 <sup>a</sup> |       |
| ≥25                                      | 301 (28.0)  | 1.01 (0.80-1.28)  |       | 1.09 (0.85-1.39)  |       |
| <b>Sex of child (1076)</b>               |             |                   | .416  |                   | .002* |
| Male                                     | 533 (49.5)  | 1.09 (0.89-1.35)  |       | 1.43 (1.14-1.77)  |       |
| Female                                   | 543 (50.5)  | 1.00 <sup>a</sup> |       | 1.00 <sup>a</sup> |       |
| <b>Gestational age at birth (1076)</b>   |             |                   | .571  |                   | .458  |
| <32 weeks                                | 5 (0.5)     | 2.21 (0.51-9.53)  |       | 1.44 (0.36-5.73)  |       |
| 32-37 weeks                              | 36 (3.4)    | 1.00 (0.56-1.78)  |       | 0.71 (0.40-1.28)  |       |
| ≥37 weeks                                | 1030 (96.2) | 1.00 <sup>a</sup> |       | 1.00 <sup>a</sup> |       |
| <b>Birth weight (1076)</b>               |             |                   | .727  |                   | .390  |
| <2500g                                   | 67 (6.2)    | 0.92 (0.59-1.44)  |       | 0.81 (0.51-1.30)  |       |
| ≥2500g                                   | 1009 (93.8) | 1.00 <sup>a</sup> |       | 1.00 <sup>a</sup> |       |
| <b>Mode of delivery (1075)</b>           |             |                   | .036* |                   | .383  |
| Cesarean                                 | 427 (39.7)  | 1.26 (1.02-1.56)  |       | 1.11 (0.88-1.39)  |       |
| Normal                                   | 648 (60.3)  | 1.00 <sup>a</sup> |       | 1.00 <sup>a</sup> |       |
| <b>APGAR score at 5 min (1075)</b>       |             |                   | .201  |                   | .598  |
| <7                                       | 4 (0.4)     | 3.39 (0.52-21.99) |       | 0.57 (0.07-4.56)  |       |
| ≥7                                       | 1071 (99.6) | 1.00 <sup>a</sup> |       | 1.00 <sup>a</sup> |       |
| <b>Duration of breastfeeding (1076)</b>  |             |                   | .745  |                   | .903  |
| No breastfeeding                         | 17 (1.6)    | 0.93 (0.42-2.05)  |       | 1.18 (0.52-2.69)  |       |
| ≤6 months                                | 148 (13.8)  | 0.89 (0.66-1.20)  |       | 1.04 (0.75-1.44)  |       |
| >6 months                                | 911 (84.7)  | 1.00 <sup>a</sup> |       | 1.00 <sup>a</sup> |       |

**Table S5.15. Adjusted associations between birth anthropometric indices and problem higher attention score (CBCL) in childhood in Pelotas**

| Variables                                | Model 2 |           |         | Model 3 |           |         | Model 4 |           |         |
|------------------------------------------|---------|-----------|---------|---------|-----------|---------|---------|-----------|---------|
|                                          | OR      | 95%CI     | p       | OR      | 95%CI     | p       | OR      | 95%CI     | p       |
| <b>Birth weight indices</b>              |         |           |         |         |           |         |         |           |         |
| BW <2500g                                | 1.32    | 1.08-1.62 | .007*   | 1.26    | 1.03-1.55 | .028*   | 1.19    | 0.94-1.51 | .140    |
| SGA                                      | 1.26    | 1.07-1.48 | .006*   | 1.22    | 1.04-1.44 | .017*   | 1.24    | 1.05-1.46 | .011*   |
| BW <10 <sup>th</sup> MGRS                | 1.27    | 1.09-1.47 | .002*   | 1.23    | 1.06-1.43 | .007*   | 1.21    | 1.03-1.43 | .023*   |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.39    | 1.14-1.70 | .001*   | 1.32    | 1.08-1.61 | .007*   | 1.37    | 1.12-1.68 | .002*   |
| <b>Stunting indices</b>                  |         |           |         |         |           |         |         |           |         |
| BL < 10 <sup>th</sup> MGRS               | 1.25    | 1.10-1.42 | .001*   | 1.22    | 1.07-1.38 | .003*   | 1.18    | 1.03-1.35 | .020*   |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.26    | 1.09-1.46 | .002*   | 1.21    | 1.05-1.41 | .011*   | 1.24    | 1.07-1.45 | .005*   |
| HC <10 <sup>th</sup> MGRS                | 1.41    | 1.21-1.65 | <.001** | 1.38    | 1.18-1.61 | <.001** | 1.39    | 1.17-1.64 | <.001** |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.31    | 1.06-1.63 | .014*   | 1.27    | 1.02-1.57 | .035*   | 1.31    | 1.05-1.63 | .018*   |
| <b>Wasting indices</b>                   |         |           |         |         |           |         |         |           |         |
| PI <10 <sup>th</sup> percentile          | 1.20    | 0.99-1.46 | .058    | 1.17    | 0.97-1.42 | .106    | 1.14    | 0.94-1.39 | .191    |
| PI-for-age <10 <sup>th</sup> percentile  | 1.04    | 0.86-1.26 | .675    | 1.03    | 0.85-1.25 | .767    | 1.05    | 0.87-1.28 | .596    |
| BMI <10 <sup>th</sup> percentile         | 1.29    | 1.06-1.57 | .011*   | 1.24    | 1.02-1.51 | .033*   | 1.19    | 0.97-1.47 | .101    |
| BMI-for-age <10 <sup>th</sup> percentile | 1.21    | 1.00-1.47 | .053    | 1.19    | 0.98-1.45 | .081    | 1.22    | 1.00-1.48 | .050    |
| <b>Asymmetry indices</b>                 |         |           |         |         |           |         |         |           |         |
| HC/BL >90 <sup>th</sup> percentile       | 1.27    | 1.05-1.54 | .013*   | 1.24    | 1.03-1.50 | .027*   | 1.21    | 0.99-1.47 | .063    |
| HC/PI >90 <sup>th</sup> percentile       | 1.04    | 0.86-1.26 | .665    | 1.04    | 0.86-1.26 | .692    | 1.03    | 0.85-1.25 | .774    |
| HC/BMI >90 <sup>th</sup> percentile      | 1.19    | 0.98-1.44 | .072    | 1.16    | .96-1.41  | .127    | 1.12    | 0.92-1.37 | .251    |

Model 2: Adjusted for maternal and demographic variables; Model 3: Adjusted for Model 2 and gestational variables; Model 4: Adjusted for Model 3 and perinatal variables; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S5.16. Adjusted associations between birth anthropometric indices and higher attention score (SDQ) in childhood in ALSPAC**

| Variables                                | Model 2 |           |         | Model 3 |           |       | Model 4 |           |       |
|------------------------------------------|---------|-----------|---------|---------|-----------|-------|---------|-----------|-------|
|                                          | OR      | 95%CI     | p       | OR      | 95%CI     | p     | OR      | 95%CI     | p     |
| <b>Birth weight indices</b>              |         |           |         |         |           |       |         |           |       |
| BW <2500g                                | 1.46    | 1.16-1.84 | .001*   | 1.34    | 1.05-1.71 | .019* | 1.13    | 0.82-1.57 | .454  |
| SGA                                      | 1.30    | 1.11-1.53 | .001*   | 1.20    | 1.01-1.42 | .038* | 1.25    | 1.00-1.55 | .047* |
| BW <10 <sup>th</sup> MGRS                | 1.33    | 1.13-1.56 | .001*   | 1.27    | 1.07-1.50 | .006* | 1.23    | 0.98-1.56 | .076  |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.38    | 1.13-1.68 | .002*   | 1.23    | 0.99-1.52 | .057  | 1.26    | 0.96-1.64 | .092  |
| <b>Stunting indices</b>                  |         |           |         |         |           |       |         |           |       |
| BL < 10 <sup>th</sup> MGRS               | 1.42    | 1.15-1.75 | .001*   | 1.33    | 1.06-1.65 | .012* | 1.36    | 1.02-1.80 | .035* |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.44    | 1.11-1.86 | .007*   | 1.29    | 0.97-1.70 | .077  | 1.38    | 0.97-1.96 | .075  |
| HC <10 <sup>th</sup> MGRS                | 1.55    | 1.24-1.93 | <.001** | 1.41    | 1.11-1.78 | .005* | 1.26    | 0.92-1.72 | .148  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.25    | 0.91-1.72 | .160    | 1.17    | 0.83-1.64 | .363  | 1.19    | 0.76-1.87 | .442  |
| <b>Wasting indices</b>                   |         |           |         |         |           |       |         |           |       |
| PI <10 <sup>th</sup> percentile          | 1.12    | 0.95-1.31 | .194    | 1.07    | 0.90-1.26 | .465  | 0.98    | 0.79-1.20 | .809  |
| PI-for-age <10 <sup>th</sup> percentile  | 1.03    | 0.88-1.21 | .706    | 1.01    | 0.85-1.19 | .950  | 1.00    | 0.82-1.23 | .993  |
| BMI <10 <sup>th</sup> percentile         | 1.14    | 0.97-1.35 | .114    | 1.08    | 0.91-1.28 | .391  | 1.04    | 0.83-1.29 | .734  |
| BMI-for-age <10 <sup>th</sup> percentile | 1.14    | 0.96-1.35 | .127    | 1.09    | 0.92-1.30 | .331  | 1.14    | 0.92-1.41 | .238  |
| <b>Asymmetry indices</b>                 |         |           |         |         |           |       |         |           |       |
| HC/BL >90 <sup>th</sup> percentile       | 1.24    | 1.05-1.45 | .010*   | 1.22    | 1.03-1.44 | .023* | 1.27    | 1.03-1.56 | .023* |
| HC/PI >90 <sup>th</sup> percentile       | 0.94    | 0.81-1.11 | .478    | 0.93    | 0.79-1.10 | .386  | 0.92    | 0.76-1.13 | .438  |
| HC/BMI >90 <sup>th</sup> percentile      | 1.13    | 0.96-1.34 | .136    | 1.08    | 0.91-1.28 | .403  | 1.06    | 0.86-1.31 | .569  |

Model 2: Adjusted for maternal and demographic variables; Model 3: Adjusted for Model 2 and gestational variables; Model 4: Adjusted for Model 3 and perinatal variables; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001



**Table S5.17. Adjusted associations between birth anthropometric indices and higher attention score (CBQ) in childhood in INTERGROWTH-21st**

| Variables                                | Model 2 |           |      | Model 3 |           |      | Model 4 |           |       |
|------------------------------------------|---------|-----------|------|---------|-----------|------|---------|-----------|-------|
|                                          | OR      | 95%CI     | p    | OR      | 95%CI     | p    | OR      | 95%CI     | p     |
| <b>Birth weight indices</b>              |         |           |      |         |           |      |         |           |       |
| BW <2500g                                | 0.82    | 0.52-1.27 | .367 | 0.82    | 0.52-1.27 | .367 | 0.57    | 0.34-0.94 | .028* |
| SGA                                      | 0.94    | 0.73-1.23 | .657 | 0.94    | 0.73-1.23 | .657 | 0.90    | 0.69-1.18 | .446  |
| BW <10 <sup>th</sup> MGRS                | 1.12    | 0.84-1.49 | .438 | 1.12    | 0.84-1.49 | .438 | 0.96    | 0.69-1.32 | .787  |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.90    | 0.65-1.25 | .537 | 0.90    | 0.65-1.25 | .537 | 0.87    | 0.62-1.22 | .422  |
| <b>Stunting indices</b>                  |         |           |      |         |           |      |         |           |       |
| BL < 10 <sup>th</sup> MGRS               | 1.04    | 0.76-1.42 | .814 | 1.04    | 0.76-1.42 | .814 | 0.87    | 0.62-1.23 | .434  |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.23    | 0.85-1.77 | .281 | 1.23    | 0.85-1.77 | .281 | 1.20    | 0.83-1.74 | .341  |
| HC <10 <sup>th</sup> MGRS                | 1.12    | 0.82-1.53 | .475 | 1.12    | 0.82-1.53 | .475 | 0.95    | 0.67-1.34 | .768  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.01    | 0.66-1.55 | .962 | 1.01    | 0.66-1.55 | .962 | 0.97    | 0.63-1.49 | .893  |
| <b>Wasting indices</b>                   |         |           |      |         |           |      |         |           |       |
| PI <10 <sup>th</sup> percentile          | 1.10    | 0.77-1.58 | .594 | 1.10    | 0.77-1.58 | .594 | 0.99    | 0.68-1.44 | .967  |
| PI-for-age <10 <sup>th</sup> percentile  | 1.21    | 0.84-1.74 | .306 | 1.21    | 0.84-1.74 | .306 | 1.18    | 0.82-1.71 | .380  |
| BMI <10 <sup>th</sup> percentile         | 1.18    | 0.83-1.68 | .352 | 1.18    | 0.83-1.68 | .352 | 1.00    | 0.68-1.48 | .986  |
| BMI-for-age <10 <sup>th</sup> percentile | 1.09    | 0.77-1.55 | .640 | 1.09    | 0.77-1.55 | .640 | 1.08    | 0.75-1.54 | .691  |
| <b>Asymmetry indices</b>                 |         |           |      |         |           |      |         |           |       |
| HC/BL >90 <sup>th</sup> percentile       | 0.94    | 0.66-1.35 | .747 | 0.94    | 0.66-1.35 | .747 | 0.88    | 0.61-1.27 | .503  |
| HC/PI >90 <sup>th</sup> percentile       | 0.95    | 0.67-1.36 | .789 | 0.95    | 0.67-1.36 | .789 | 0.87    | 0.61-1.26 | .464  |
| HC/BMI >90 <sup>th</sup> percentile      | 0.94    | 0.65-1.34 | .712 | 0.94    | 0.65-1.34 | .712 | 0.81    | 0.56-1.17 | .261  |

Model 2: Adjusted for maternal and demographic variables; Model 3: Adjusted for Model 2 and gestational variables; Model 4: Adjusted for Model 3 and perinatal variables; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S5.18. Adjusted associations between birth anthropometric indices and lower cognitive score (WPPSI) in childhood in Pelotas**

| Variables                                | Model 2 |           |         | Model 3 |           |         | Model 4 |           |         |
|------------------------------------------|---------|-----------|---------|---------|-----------|---------|---------|-----------|---------|
|                                          | OR      | 95%CI     | p       | OR      | 95%CI     | p       | OR      | 95%CI     | p       |
| <b>Birth weight indices</b>              |         |           |         |         |           |         |         |           |         |
| BW <2500g                                | 1.64    | 1.33-2.03 | <.001** | 1.66    | 1.34-2.06 | <.001** | 1.43    | 1.13-1.82 | .003*   |
| SGA                                      | 1.39    | 1.18-1.65 | <.001** | 1.43    | 1.21-1.69 | <.001** | 1.42    | 1.20-1.69 | <.001** |
| BW <10 <sup>th</sup> MGRS                | 1.48    | 1.27-1.73 | <.001** | 1.52    | 1.30-1.78 | <.001** | 1.38    | 1.16-1.64 | <.001** |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.45    | 1.18-1.77 | <.001** | 1.48    | 1.21-1.82 | <.001** | 1.54    | 1.25-1.90 | <.001** |
| <b>Stunting indices</b>                  |         |           |         |         |           |         |         |           |         |
| BL < 10 <sup>th</sup> MGRS               | 1.41    | 1.23-1.61 | <.001** | 1.44    | 1.25-1.64 | <.001** | 1.33    | 1.15-1.54 | <.001** |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.36    | 1.17-1.59 | <.001** | 1.41    | 1.20-1.64 | <.001** | 1.47    | 1.5-1.72  | <.001** |
| HC <10 <sup>th</sup> MGRS                | 1.77    | 1.50-2.09 | <.001** | 1.81    | 1.53-2.14 | <.001** | 1.66    | 1.38-1.98 | <.001** |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.80    | 1.43-2.27 | <.001** | 1.84    | 1.46-2.32 | <.001** | 1.83    | 1.44-2.30 | <.001** |
| <b>Wasting indices</b>                   |         |           |         |         |           |         |         |           |         |
| PI <10 <sup>th</sup> percentile          | 1.43    | 1.18-1.75 | <.001** | 1.45    | 1.19-1.77 | <.001** | 1.32    | 1.07-1.61 | .008*   |
| PI-for-age <10 <sup>th</sup> percentile  | 1.11    | 0.91-1.36 | .314    | 1.12    | 0.91-1.37 | .279    | 1.12    | 0.91-1.37 | .292    |
| BMI <10 <sup>th</sup> percentile         | 1.66    | 1.35-2.03 | <.001** | 1.68    | 1.37-2.07 | <.001** | 1.49    | 1.20-1.86 | <.001** |
| BMI-for-age <10 <sup>th</sup> percentile | 1.22    | 1.00-1.49 | .052    | 1.25    | 1.03-1.53 | .028*   | 1.23    | 1.00-1.51 | .047*   |
| <b>Asymmetry indices</b>                 |         |           |         |         |           |         |         |           |         |
| HC/BL >90 <sup>th</sup> percentile       | 1.28    | 1.05-1.57 | .017*   | 1.26    | 1.03-1.55 | .023*   | 1.24    | 1.01-1.52 | .042*   |
| HC/PI >90 <sup>th</sup> percentile       | 1.02    | 0.84-1.25 | .814    | 1.03    | 0.85-1.26 | .743    | 1.00    | 0.82-1.23 | .987    |
| HC/BMI >90 <sup>th</sup> percentile      | 1.47    | 1.20-1.80 | <.001** | 1.49    | 1.22-1.83 | <.001** | 1.37    | 1.11-1.69 | .004*   |

Model 2: Adjusted for maternal and demographic variables; Model 3: Adjusted for Model 2 and gestational variables; Model 4: Adjusted for Model 3 and perinatal variables; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S5.19. Adjusted associations between birth anthropometric indices and lower cognitive score (WPPSI) in childhood in ALSPAC**

| Variables                                | Model 2 |           |       | Model 3 |           |       | Model 4 |           |       |
|------------------------------------------|---------|-----------|-------|---------|-----------|-------|---------|-----------|-------|
|                                          | OR      | 95%CI     | p     | OR      | 95%CI     | p     | OR      | 95%CI     | p     |
| <b>Birth weight indices</b>              |         |           |       |         |           |       |         |           |       |
| BW <2500g                                | 1.48    | 0.71-3.10 | .295  | 1.43    | 0.66-3.09 | .365  | 1.95    | 0.81-4.73 | .139  |
| SGA                                      | 1.28    | 0.77-2.11 | .337  | 1.44    | 0.85-2.45 | .181  | 1.50    | 0.86-2.61 | .156  |
| BW <10 <sup>th</sup> MGRS                | 1.82    | 1.11-2.98 | .017* | 1.83    | 1.10-3.06 | .020* | 2.53    | 1.43-4.47 | .002* |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.77    | 0.95-3.31 | .074  | 1.76    | 0.91-3.42 | .094  | 1.92    | 0.97-3.81 | .061  |
| <b>Stunting indices</b>                  |         |           |       |         |           |       |         |           |       |
| BL < 10 <sup>th</sup> MGRS               | 1.63    | 0.89-2.98 | .114  | 1.62    | 0.86-3.03 | .133  | 2.00    | 1.01-3.97 | .047* |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.89    | 0.81-4.39 | .141  | 1.72    | 0.68-4.31 | .251  | 1.79    | 0.70-4.56 | .226  |
| HC <10 <sup>th</sup> MGRS                | 1.64    | 0.81-3.32 | .166  | 1.46    | 0.71-3.00 | .308  | 1.96    | 0.88-4.34 | .098  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.43    | 0.99-5.93 | .051  | 2.04    | 0.82-5.09 | .125  | 2.41    | 0.95-6.13 | .065  |
| <b>Wasting indices</b>                   |         |           |       |         |           |       |         |           |       |
| PI <10 <sup>th</sup> percentile          | 1.15    | 0.77-1.73 | .492  | 1.15    | 0.75-1.74 | .526  | 1.31    | 0.81-2.10 | .270  |
| PI-for-age <10 <sup>th</sup> percentile  | 1.09    | 0.72-1.64 | .678  | 1.17    | 0.76-1.79 | .482  | 1.31    | 0.81-2.11 | .276  |
| BMI <10 <sup>th</sup> percentile         | 1.12    | 0.74-1.69 | .597  | 1.14    | 0.74-1.75 | .560  | 1.37    | 0.85-2.22 | .193  |
| BMI-for-age <10 <sup>th</sup> percentile | 1.09    | 0.70-1.70 | .696  | 1.21    | 0.77-1.92 | .407  | 1.37    | 0.84-2.24 | .209  |
| <b>Asymmetry indices</b>                 |         |           |       |         |           |       |         |           |       |
| HC/BL >90 <sup>th</sup> percentile       | 0.82    | 0.48-1.40 | .474  | 0.95    | 0.55-1.66 | .861  | 1.01    | 0.56-1.80 | .984  |
| HC/PI >90 <sup>th</sup> percentile       | 1.10    | 0.74-1.64 | .636  | 1.09    | 0.71-1.66 | .704  | 1.17    | 0.74-1.87 | .500  |
| HC/BMI >90 <sup>th</sup> percentile      | 1.20    | 0.79-1.81 | .395  | 1.2     | 0.79-1.88 | .372  | 1.41    | 0.87-2.28 | .166  |

Model 2: Adjusted for maternal and demographic variables; Model 3: Adjusted for Model 2 and gestational variables; Model 4: Adjusted for Model 3 and perinatal variables; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S5.20. Adjusted associations between birth anthropometric indices and lower cognitive score (INTER-NDA) in childhood in INTERGROWTH-21st**

| Variables                                | Model 2 |           |      | Model 3 |           |      | Model 4 |           |       |
|------------------------------------------|---------|-----------|------|---------|-----------|------|---------|-----------|-------|
|                                          | OR      | 95%CI     | p    | OR      | 95%CI     | p    | OR      | 95%CI     | p     |
| <b>Birth weight indices</b>              |         |           |      |         |           |      |         |           |       |
| BW <2500g                                | 1.00    | 0.97-1.20 | .231 | 1.00    | 0.97-1.20 | .231 | 0.66    | 0.38-1.15 | .143  |
| SGA                                      | 0.91    | 0.69-1.21 | .531 | 0.91    | 0.69-1.21 | .531 | 0.90    | 0.68-1.20 | .483  |
| BW <10 <sup>th</sup> MGRS                | 0.90    | 0.67-1.22 | .497 | 0.90    | 0.67-1.22 | .497 | 0.88    | 0.63-1.24 | .460  |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.06    | 0.75-1.50 | .742 | 1.06    | 0.75-1.50 | .742 | 1.07    | 0.75-1.53 | .714  |
| <b>Stunting indices</b>                  |         |           |      |         |           |      |         |           |       |
| BL < 10 <sup>th</sup> MGRS               | 0.72    | 0.52-1.00 | .052 | 0.72    | 0.52-1.00 | .052 | 0.67    | 0.46-0.95 | .027* |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.91    | 0.63-1.32 | .633 | 0.91    | 0.63-1.32 | .633 | 0.91    | 0.62-1.32 | .605  |
| HC <10 <sup>th</sup> MGRS                | 1.00    | 0.71-1.41 | .992 | 1.00    | 0.71-1.41 | .992 | 1.00    | 0.68-1.46 | .983  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.03    | 0.65-1.63 | .898 | 1.03    | 0.65-1.63 | .898 | 1.03    | 0.64-1.64 | .906  |
| <b>Wasting indices</b>                   |         |           |      |         |           |      |         |           |       |
| PI <10 <sup>th</sup> percentile          | 1.36    | 0.92-2.02 | .125 | 1.36    | 0.92-2.02 | .125 | 1.31    | 0.87-1.97 | .195  |
| PI-for-age <10 <sup>th</sup> percentile  | 1.43    | 0.98-2.11 | .067 | 1.43    | 0.98-2.11 | .067 | 1.43    | 0.96-2.12 | .079  |
| BMI <10 <sup>th</sup> percentile         | 1.43    | 0.96-2.10 | .072 | 1.43    | 0.96-2.10 | .072 | 1.44    | 0.94-2.20 | .098  |
| BMI-for-age <10 <sup>th</sup> percentile | 1.21    | 0.84-1.76 | .312 | 1.21    | 0.84-1.76 | .312 | 1.18    | 0.81-1.74 | .390  |
| <b>Asymmetry indices</b>                 |         |           |      |         |           |      |         |           |       |
| HC/BL >90 <sup>th</sup> percentile       | 0.92    | 0.64-1.33 | .661 | 0.92    | 0.64-1.33 | .661 | 0.90    | 0.62-1.32 | .600  |
| HC/PI >90 <sup>th</sup> percentile       | 1.41    | 0.96-2.07 | .077 | 1.41    | 0.96-2.07 | .077 | 1.32    | 0.90-1.96 | .161  |
| HC/BMI >90 <sup>th</sup> percentile      | 1.11    | 0.75-1.65 | .610 | 1.11    | 0.75-1.65 | .610 | 1.06    | 0.71-1.60 | .767  |

Model 2: Adjusted for maternal and demographic variables; Model 3: Adjusted for Model 2 and gestational variables; Model 4: Adjusted for Model 3 and perinatal variables; BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S5.21. Adjusted associations between birth anthropometric indices and problem attention scores (dichotomous) in childhood in Pelotas**

| Variables                                | Unadjusted |           |         | Fully adjusted |           |       |
|------------------------------------------|------------|-----------|---------|----------------|-----------|-------|
|                                          | OR         | 95%CI     | p       | OR             | 95%CI     | p     |
| <b>Birth weight indices</b>              |            |           |         |                |           |       |
| BW <2500g                                | 1.70       | 1.18-2.44 | .004*   | 1.43           | 0.89-2.30 | .135  |
| SGA                                      | 1.84       | 1.36-2.47 | <.001** | 1.76           | 1.25-2.48 | .001* |
| BW <10 <sup>th</sup> MGRS                | 1.58       | 1.19-2.10 | .002*   | 1.46           | 1.02-2.08 | .041* |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.18       | 1.56-3.04 | <.001*  | 1.95           | 1.33-2.87 | .001* |
| <b>Stunting indices</b>                  |            |           |         |                |           |       |
| BL < 10 <sup>th</sup> MGRS               | 1.50       | 1.16-1.95 | .002*   | 1.35           | 0.98-1.86 | .067  |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.67       | 1.26-2.20 | <.001** | 1.45           | 1.04-2.01 | .029* |
| HC <10 <sup>th</sup> MGRS                | 1.56       | 1.15-2.10 | .004*   | 1.21           | 0.83-1.77 | .327  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.24       | 0.80-1.93 | .332    | 0.84           | 0.52-1.38 | .499  |
| <b>Wasting indices</b>                   |            |           |         |                |           |       |
| PI <10 <sup>th</sup> percentile          | 1.47       | 1.02-2.11 | .040*   | 1.33           | 0.88-2.01 | .172  |
| PI-for-age <10 <sup>th</sup> percentile  | 1.32       | 0.90-1.93 | .153    | 1.28           | 0.84-1.96 | .246  |
| BMI <10 <sup>th</sup> percentile         | 1.63       | 1.15-2.33 | .007*   | 1.36           | 0.88-2.08 | .163  |
| BMI-for-age <10 <sup>th</sup> percentile | 1.27       | 0.86-1.86 | .231    | 1.12           | 0.73-1.73 | .598  |
| <b>Asymmetry indices</b>                 |            |           |         |                |           |       |
| HC/BL >90 <sup>th</sup> percentile       | 1.43       | 0.99-2.07 | .055    | 1.49           | 0.98-2.28 | .064  |
| HC/PI >90 <sup>th</sup> percentile       | 1.18       | 0.80-1.74 | .412    | 1.22           | 0.79-1.90 | .370  |
| HC/BMI >90 <sup>th</sup> percentile      | 1.42       | 0.98-2.05 | .062    | 1.34           | 0.88-2.05 | .173  |

Impairment = CBCL *t* score ≥67; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S5.22. Adjusted associations between birth anthropometric indices and problem attention scores (dichotomous) in childhood in ALSPAC**

| Variables                                | Unadjusted |           |          | Fully adjusted |            |          |
|------------------------------------------|------------|-----------|----------|----------------|------------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI      | <i>p</i> |
| <b>Birth weight indices</b>              |            |           |          |                |            |          |
| BW <2500g                                | 1.47       | 1.05-2.06 | .025*    | 1.27           | 0.29-5.56  | .754     |
| SGA                                      | 1.52       | 1.20-1.93 | .001*    | 2.91           | 1.18-7.17  | .020*    |
| BW <10 <sup>th</sup> MGRS                | 1.62       | 1.30-2.03 | <.001**  | 2.62           | 1.03-6.61  | .042*    |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.57       | 1.18-2.08 | .002*    | 2.19           | 0.72-6.64  | .168     |
| <b>Stunting indices</b>                  |            |           |          |                |            |          |
| BL < 10 <sup>th</sup> MGRS               | 1.80       | 1.35-2.39 | <.001**  | 3.99           | 1.44-11.04 | .008*    |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.00       | 1.43-2.80 | <.001**  | 2.18           | 0.61-7.85  | .234     |
| HC <10 <sup>th</sup> MGRS                | 1.82       | 1.35-2.47 | <.001**  | 2.11           | 0.55-8.15  | .278     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.19       | 0.72-1.96 | .495     | 0.79           | 0.13-4.72  | .795     |
| <b>Wasting indices</b>                   |            |           |          |                |            |          |
| PI <10 <sup>th</sup> percentile          | 1.21       | 0.94-1.56 | .141     | 1.01           | 0.38-2.65  | .989     |
| PI-for-age <10 <sup>th</sup> percentile  | 1.02       | 0.78-1.34 | .877     | 0.95           | 0.36-2.55  | .923     |
| BMI <10 <sup>th</sup> percentile         | 1.37       | 1.06-1.75 | .015*    | 1.41           | 0.58-3.43  | .454     |
| BMI-for-age <10 <sup>th</sup> percentile | 1.46       | 1.14-1.87 | .003*    | 1.40           | 0.57-3.43  | .459     |
| <b>Asymmetry indices</b>                 |            |           |          |                |            |          |
| HC/BL >90 <sup>th</sup> percentile       | 1.16       | 0.89-1.50 | .275     | 2.22           | 0.90-5.42  | .082     |
| HC/PI >90 <sup>th</sup> percentile       | 0.83       | 0.62-1.10 | .197     | 1.00           | 0.35-2.81  | .994     |
| HC/BMI >90 <sup>th</sup> percentile      | 1.26       | 0.98-1.62 | .077     | 1.41           | 0.57-3.54  | .459     |

Impairment = SDQ score  $\geq 7$ ; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* =  $p < .05$ ; \*\*= $p < .001$

**Table S5.23. Adjusted associations between birth anthropometric indices and problem attention scores (dichotomous) in childhood in INTERGROWTH-21st**

| Variables                                | Unadjusted |           |          | Fully adjusted |           |          |
|------------------------------------------|------------|-----------|----------|----------------|-----------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI     | <i>p</i> |
| <b>Birth weight indices</b>              |            |           |          |                |           |          |
| BW <2500g                                | 0.24       | 0.03-1.76 | .161     | 1.00           | 0.49-2.02 | .998     |
| SGA                                      | 0.92       | 0.48-1.76 | .790     | 0.87           | 0.44-1.74 | .697     |
| BW <10 <sup>th</sup> MGRS                | 1.28       | 0.67-2.41 | .455     | 1.51           | 0.69-3.28 | .302     |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.12       | 0.52-2.42 | .773     | 1.14           | 0.51-2.57 | .748     |
| <b>Stunting indices</b>                  |            |           |          |                |           |          |
| BL < 10 <sup>th</sup> MGRS               | 0.95       | 0.45-2.00 | .885     | 1.11           | 0.48-2.58 | .805     |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.93       | 0.95-3.93 | .071     | 2.17           | 1.00-4.72 | .051     |
| HC <10 <sup>th</sup> MGRS                | 1.07       | 0.51-2.22 | .861     | 0.82           | 0.35-1.90 | .646     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.81       | 0.79-4.13 | .162     | 1.45           | 0.61-3.44 | .402     |
| <b>Wasting indices</b>                   |            |           |          |                |           |          |
| PI <10 <sup>th</sup> percentile          | 0.96       | 0.40-2.31 | .934     | 0.75           | 0.28-2.03 | .576     |
| PI-for-age <10 <sup>th</sup> percentile  | 1.22       | 0.54-2.77 | .635     | 1.24           | 0.52-2.93 | .631     |
| BMI <10 <sup>th</sup> percentile         | 0.61       | 0.22-1.72 | .347     | 0.45           | 0.12-1.56 | .206     |
| BMI-for-age <10 <sup>th</sup> percentile | 0.95       | 0.40-2.27 | .906     | 0.87           | 0.35-2.17 | .765     |
| <b>Asymmetry indices</b>                 |            |           |          |                |           |          |
| HC/BL >90 <sup>th</sup> percentile       | 1.30       | 0.57-2.95 | .535     | 1.37           | 0.53-3.53 | .517     |
| HC/PI >90 <sup>th</sup> percentile       | 1.15       | 0.50-2.60 | .747     | 0.92           | 0.36-2.33 | .861     |
| HC/BMI >90 <sup>th</sup> percentile      | 0.95       | 0.40-2.28 | .915     | 0.88           | 0.32-2.42 | .798     |

Impairment = CBCL *t* score ≥67; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = *p*<.05; \*\*=*p*<.001

**Table S5.24. Adjusted associations between birth anthropometric indices and problem cognitive scores (dichotomous) in childhood in Pelotas**

| Variables                                | Unadjusted |           |         | Fully adjusted |           |         |
|------------------------------------------|------------|-----------|---------|----------------|-----------|---------|
|                                          | OR         | 95%CI     | p       | OR             | 95%CI     | p       |
| <b>Birth weight indices</b>              |            |           |         |                |           |         |
| BW <2500g                                | 2.17       | 1.70-2.78 | <.001** | 1.20           | 0.86-1.68 | .277    |
| SGA                                      | 1.67       | 1.35-2.06 | <.001** | 1.27           | 0.99-1.63 | .060    |
| BW <10 <sup>th</sup> MGRS                | 1.99       | 1.63-2.42 | <.001** | 1.21           | 0.93-1.58 | .152    |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.82       | 1.42-2.32 | <.001** | 1.39           | 1.04-1.85 | .027*   |
| <b>Stunting indices</b>                  |            |           |         |                |           |         |
| BL < 10 <sup>th</sup> MGRS               | 1.73       | 1.45-2.08 | <.001** | 1.16           | 0.92-1.45 | .222    |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.70       | 1.39-2.08 | <.001** | 1.30           | 1.02-1.66 | .032*   |
| HC <10 <sup>th</sup> MGRS                | 2.38       | 1.96-2.90 | <.001** | 1.59           | 1.23-2.05 | <.001** |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.32       | 1.78-3.03 | <.001** | 1.69           | 1.24-2.30 | .001*   |
| <b>Wasting indices</b>                   |            |           |         |                |           |         |
| PI <10 <sup>th</sup> percentile          | 1.57       | 1.21-2.03 | .001*   | 1.21           | 0.89-1.63 | .231    |
| PI-for-age <10 <sup>th</sup> percentile  | 1.19       | 0.90-1.57 | .221    | 1.02           | 0.74-1.40 | .920    |
| BMI <10 <sup>th</sup> percentile         | 2.16       | 1.69-2.76 | <.001** | 1.36           | 1.00-1.86 | .052    |
| BMI-for-age <10 <sup>th</sup> percentile | 1.39       | 1.06-1.81 | .017*   | 1.09           | 0.80-1.49 | .568    |
| <b>Asymmetry indices</b>                 |            |           |         |                |           |         |
| HC/BL >90 <sup>th</sup> percentile       | 1.45       | 1.11-1.89 | .006*   | 1.32           | 0.97-1.79 | .074    |
| HC/PI >90 <sup>th</sup> percentile       | 0.99       | 0.74-1.32 | .932    | 0.99           | 0.71-1.37 | .942    |
| HC/BMI >90 <sup>th</sup> percentile      | 1.74       | 1.35-2.25 | <.001** | 1.37           | 1.01-1.86 | .043*   |

Impairment = WPPSI score >1SD below mean; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001



**Table S5.25. Adjusted associations between birth anthropometric indices and problem cognitive scores (dichotomous) in childhood in ALSPAC**

| Variables                                | Unadjusted |           |      | Fully adjusted |            |      |
|------------------------------------------|------------|-----------|------|----------------|------------|------|
|                                          | OR         | 95%CI     | p    | OR             | 95%CI      | p    |
| <b>Birth weight indices</b>              |            |           |      |                |            |      |
| BW <2500g                                | 0.45       | 0.60-3.36 | .436 | 1.00           | 0.01-9.99  | .999 |
| SGA                                      | 0.83       | 0.29-2.36 | .731 | 0.64           | 0.13-3.24  | .585 |
| BW <10 <sup>th</sup> MGRS                | 1.01       | 0.52-1.96 | .988 | 1.87           | 0.64-5.46  | .255 |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.62       | 0.15-2.60 | .508 | 0.69           | 0.07-6.48  | .746 |
| <b>Stunting indices</b>                  |            |           |      |                |            |      |
| BL < 10 <sup>th</sup> MGRS               | 0.96       | 0.42-2.17 | .913 | 0.61           | 0.12-3.00  | .540 |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.59       | 0.63-4.00 | .328 | 1.01           | 0.19-5.45  | .988 |
| HC <10 <sup>th</sup> MGRS                | 1.11       | 0.33-3.71 | .862 | 1.35           | 0.20-8.96  | .759 |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.34       | 0.67-8.14 | .183 | 3.17           | 0.45-21.91 | .242 |
| <b>Wasting indices</b>                   |            |           |      |                |            |      |
| PI <10 <sup>th</sup> percentile          | 1.20       | 0.72-2.02 | .489 | 1.27           | 0.50-3.22  | .620 |
| PI-for-age <10 <sup>th</sup> percentile  | 1.08       | 0.63-1.84 | .791 | 1.51           | 0.63-3.63  | .359 |
| BMI <10 <sup>th</sup> percentile         | 0.96       | 0.54-1.71 | .884 | 1.35           | 0.49-3.72  | .559 |
| BMI-for-age <10 <sup>th</sup> percentile | 1.26       | 0.73-2.16 | .409 | 2.23           | 0.97-5.12  | .059 |
| <b>Asymmetry indices</b>                 |            |           |      |                |            |      |
| HC/BL >90 <sup>th</sup> percentile       | 0.92       | 0.45-1.92 | .833 | 0.71           | 0.20-2.56  | .601 |
| HC/PI >90 <sup>th</sup> percentile       | 0.98       | 0.56-1.72 | .940 | 1.11           | 0.42-2.89  | .835 |
| HC/BMI >90 <sup>th</sup> percentile      | 1.10       | 0.63-1.92 | .730 | 1.53           | 0.60-3.89  | .371 |

Impairment = WPPSI score >1SD below mean; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S5.26. Adjusted associations between birth anthropometric indices and problem cognitive scores (dichotomous) in childhood in INTERGROWTH-21<sup>st</sup>**

| Variables                                | Unadjusted |           |          | Fully adjusted |           |          |
|------------------------------------------|------------|-----------|----------|----------------|-----------|----------|
|                                          | OR         | 95%CI     | <i>p</i> | OR             | 95%CI     | <i>p</i> |
| <b>Birth weight indices</b>              |            |           |          |                |           |          |
| BW <2500g                                | 0.96       | 0.53-1.73 | .881     | 0.85           | 0.42-1.70 | .642     |
| SGA                                      | 0.93       | 0.64-1.33 | .674     | 0.84           | 0.57-1.23 | .366     |
| BW <10 <sup>th</sup> MGRS                | 1.07       | 0.73-1.56 | .723     | 1.00           | 0.64-1.57 | .996     |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.12       | 0.72-1.73 | .624     | 1.00           | 0.63-1.59 | .999     |
| <b>Stunting indices</b>                  |            |           |          |                |           |          |
| BL < 10 <sup>th</sup> MGRS               | 0.66       | 0.41-1.05 | .080     | 0.61           | 0.37-1.03 | .064     |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.79       | 0.47-1.31 | .354     | 0.76           | 0.45-1.29 | .304     |
| HC <10 <sup>th</sup> MGRS                | 1.40       | 0.94-2.07 | .098     | 1.35           | 0.85-2.14 | .203     |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.27       | 0.74-2.20 | .387     | 1.11           | 0.63-1.97 | .711     |
| <b>Wasting indices</b>                   |            |           |          |                |           |          |
| PI <10 <sup>th</sup> percentile          | 1.66       | 1.06-2.62 | .027*    | 1.51           | 0.92-2.48 | .104     |
| PI-for-age <10 <sup>th</sup> percentile  | 1.52       | 0.96-2.40 | .075     | 1.36           | 0.84-2.21 | .217     |
| BMI <10 <sup>th</sup> percentile         | 1.62       | 1.04-2.54 | .035*    | 1.48           | 0.88-2.47 | .136     |
| BMI-for-age <10 <sup>th</sup> percentile | 1.25       | 0.79-1.98 | .350     | 1.09           | 0.67-1.77 | .742     |
| <b>Asymmetry indices</b>                 |            |           |          |                |           |          |
| HC/BL >90 <sup>th</sup> percentile       | 0.81       | 0.48-1.37 | .428     | 0.78           | 0.44-1.35 | .367     |
| HC/PI >90 <sup>th</sup> percentile       | 1.49       | 0.94-2.36 | .088     | 1.39           | 0.85-2.28 | .195     |
| HC/BMI >90 <sup>th</sup> percentile      | 1.40       | 0.88-2.23 | .151     | 1.34           | 0.80-2.24 | .265     |

Impairment = INTER-NDA score >1SD below mean; Fully adjusted model: Adjusted for maternal and demographic variables, gestational variables, perinatal variables and child nutrition/mother-child morbidity; \* BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21<sup>st</sup> = INTERGROWTH-21<sup>st</sup> growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = *p*<.05; \*\*=*p*<.001

## Chapter 6

Table S6.1. Site interaction effects (birth index\*site) for attention (CBQ) and cognitive (INTER-NDA) outcomes

| Variable                                 | Attention |           |       | Cognition |           |       |
|------------------------------------------|-----------|-----------|-------|-----------|-----------|-------|
|                                          | OR        | 95%CI     | p     | OR        | 95%CI     | p     |
| <b>Birth weight indices</b>              |           |           |       |           |           |       |
| BW <2500g                                | 0.89      | 0.81-0.98 | .021* | 0.92      | 0.83-1.02 | .099  |
| SGA                                      | 0.89      | 0.84-0.95 | .001* | 0.95      | 0.89-1.02 | .156  |
| BW <10 <sup>th</sup> MGRS                | 0.91      | 0.85-0.98 | .008* | 0.93      | 0.87-1.01 | .080  |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.88      | 0.82-0.96 | .002* | 0.97      | 0.90-1.05 | .442  |
| <b>Stunting indices</b>                  |           |           |       |           |           |       |
| BL < 10 <sup>th</sup> MGRS               | 0.90      | 0.84-0.97 | .006* | 0.91      | 0.84-0.98 | .016* |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.90      | 0.84-0.97 | .017* | 0.95      | 0.88-1.04 | .280  |
| HC <10 <sup>th</sup> MGRS                | 0.92      | 0.85-1.00 | .037* | 0.94      | 0.86-1.02 | .143  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.92      | 0.85-1.00 | .040* | 0.96      | 0.86-1.07 | .426  |
| <b>Wasting indices</b>                   |           |           |       |           |           |       |
| PI <10 <sup>th</sup> percentile          | 0.91      | 0.91-0.98 | .018* | 1.01      | 0.92-1.10 | .877  |
| PI-for-age <10 <sup>th</sup> percentile  | 0.91      | 0.84-0.99 | .024* | 1.02      | 0.94-1.11 | .656  |
| BMI <10 <sup>th</sup> percentile         | 0.93      | 0.85-1.01 | .080  | 1.02      | 0.94-1.12 | .619  |
| BMI-for-age <10 <sup>th</sup> percentile | 0.90      | 0.83-0.97 | .008* | 0.98      | 0.91-1.07 | .712  |
| <b>Asymmetry indices</b>                 |           |           |       |           |           |       |
| HC/BL >90 <sup>th</sup> percentile       | 0.88      | 0.82-0.95 | .001* | 0.97      | 0.90-1.05 | .413  |
| HC/PI >90 <sup>th</sup> percentile       | 0.89      | 0.82-0.96 | .004* | 1.02      | 0.94-1.12 | .591  |
| HC/BMI >90 <sup>th</sup> percentile      | 0.88      | 0.81-0.96 | .003* | 1.00      | 0.91-1.09 | .918  |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21st = INTERGROWTH-21st growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S6.2. Descriptive statistics (*M*, *SD*), frequencies (*n*, %), ANOVA and chi-squared analyses comparing INTERGROWTH-21<sup>st</sup> sites on maternal and child characteristics**

| Variables                        | UK (N=174)                | Italy (N=205)             | Brazil (N=113)            | India (N=282)             | Kenya (N=339)             | F/ $\chi^2$ | <i>p</i> |
|----------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|-------------|----------|
| Maternal school (years)          | 16.26 (2.99) <sup>1</sup> | 13.79 (4.02) <sup>3</sup> | 13.86 (3.21) <sup>3</sup> | 16.14 (1.24) <sup>1</sup> | 15.52 (1.31) <sup>2</sup> | 43.08       | <.001**  |
| Maternal age at delivery (years) | 30.58 (3.24) <sup>1</sup> | 29.25 (4.31) <sup>2</sup> | 28.75 (4.02) <sup>2</sup> | 27.15 (3.54) <sup>3</sup> | 29.06 (3.58) <sup>2</sup> | 25.22       | <.001**  |
| Maternal BMI                     | 23.41 (2.74) <sup>1</sup> | 22.61 (2.73) <sup>2</sup> | 24.03 (2.86) <sup>1</sup> | 22.46 (3.07) <sup>2</sup> | 24.03 (3.08) <sup>1</sup> | 15.95       | <.001**  |
| Preterm delivery (<37 weeks)     | 5 (2.9%)                  | 8 (3.8%)                  | 6 (5.3%)                  | 17 (6.0%)                 | 10 (2.9%)                 | 4.95        | .292     |
| Cesarean section                 | 28 (16.1%)                | 48 (22.3%)                | 97 (85.8%)                | 155 (55.2%)               | 116 (33.9%)               | 201.33      | <.001**  |
| Child sex (male)                 | 91 (52.3%)                | 104 (48.4%)               | 60 (53.1%)                | 122 (43.3%)               | 180 (52.6%)               | 6.97        | .137     |
| APGAR score <7                   | 1 (0.6%)                  | 0 (0.0%)                  | 1 (0.9%)                  | 0 (0.0%)                  | 2 (0.6%)                  | 3.42        | .491     |
| Breastfeed <6 months             | 55 (31.6%)                | 69 (32.1%)                | 28 (24.8%)                | 6 (2.1%)                  | 22 (6.4%)                 | 160.58      | <.001**  |
| Birth weight (g)                 | 3457 (523) <sup>1</sup>   | 3255 (475) <sup>2</sup>   | 3231 (473) <sup>2</sup>   | 2902 (414) <sup>3</sup>   | 3217 (474) <sup>2</sup>   | 42.27       | <.001**  |
| Birth length (cm)                | 50.00 (1.99) <sup>1</sup> | 49.42 (2.28) <sup>2</sup> | 48.51 (2.26) <sup>3</sup> | 48.58 (1.81) <sup>3</sup> | 48.93 (2.13) <sup>3</sup> | 16.33       | <.001**  |
| Head circumference (cm)          | 34.40 (1.51) <sup>1</sup> | 34.12 (1.38) <sup>1</sup> | 34.01 (1.55) <sup>1</sup> | 33.11 (1.14) <sup>2</sup> | 34.16 (1.41) <sup>1</sup> | 33.45       | <.001**  |
| Ponderal index                   | 2.77 (0.22) <sup>1</sup>  | 2.68 (0.22) <sup>2</sup>  | 2.81 (0.24) <sup>1</sup>  | 2.52 (0.27) <sup>3</sup>  | 2.73 (0.26) <sup>2</sup>  | 44.91       | <.001**  |
| Body mass index                  | 13.85 (1.21) <sup>1</sup> | 13.26 (1.20) <sup>1</sup> | 13.65 (1.31) <sup>1</sup> | 12.26 (1.31) <sup>2</sup> | 13.36 (1.35) <sup>1</sup> | 52.94       | <.001**  |

<sup>1,2,3</sup> Ryan-Einot-Gabriel-Welsch Range (REGWQ) post-hoc analyses homogeneous subsets; \* = *p*<.05; \*\*=*p*<.001

**Table S6.3. Unadjusted associations between birth growth indices and problem attention score (continuous) in childhood in UK, Italy and Brazil combined and in India and Kenya combined**

| Variables                                | UK, Italy and Brazil |       | India and Kenya  |      |
|------------------------------------------|----------------------|-------|------------------|------|
|                                          | OR (95%CI)           | p     | OR (95%CI)       | p    |
| <b>Birth weight indices</b>              |                      |       |                  |      |
| BW <2500g                                | 2.47 (0.97-6.31)     | .059  | 0.67 (0.41-1.11) | .118 |
| SGA                                      | 0.84 (0.52-1.35)     | .467  | 1.01 (0.74-1.38) | .954 |
| BW <10 <sup>th</sup> MGRS                | 1.03 (0.61-1.76)     | .901  | 1.17 (0.84-1.63) | .344 |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.77 (0.41-1.45)     | .422  | 0.99 (0.67-1.45) | .947 |
| <b>Stunting indices</b>                  |                      |       |                  |      |
| BL < 10 <sup>th</sup> MGRS               | 1.57 (0.92-2.68)     | .097  | 0.77 (0.52-1.14) | .187 |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.77 (0.91-3.45)     | .091  | 1.01 (0.65-1.57) | .963 |
| HC <10 <sup>th</sup> MGRS                | 2.15 (1.16-4.00)     | .016* | 1.01 (0.71-1.44) | .963 |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.11 (0.81-5.46)     | .125  | 0.93 (0.58-1.49) | .755 |
| <b>Wasting indices</b>                   |                      |       |                  |      |
| PI <10 <sup>th</sup> percentile          | 1.11 (0.48-2.60)     | .803  | 1.13 (0.77-1.68) | .532 |
| PI-for-age <10 <sup>th</sup> percentile  | 1.22 (0.57-2.62)     | .604  | 1.29 (0.85-1.94) | .229 |
| BMI <10 <sup>th</sup> percentile         | 1.74 (0.75-4.05)     | .197  | 1.14 (0.78-1.68) | .502 |
| BMI-for-age <10 <sup>th</sup> percentile | 1.02 (0.48-2.14)     | .970  | 1.19 (0.80-1.77) | .383 |
| <b>Asymmetry indices</b>                 |                      |       |                  |      |
| HC/BL >90 <sup>th</sup> percentile       | 0.63 (0.37-1.06)     | .080  | 1.05 (0.65-1.72) | .834 |
| HC/PI >90 <sup>th</sup> percentile       | 1.00 (0.45-2.22)     | .999  | 0.96 (0.65-1.43) | .847 |
| HC/BMI >90 <sup>th</sup> percentile      | 0.65 (0.29-1.46)     | .298  | 1.01 (0.68-1.50) | .959 |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21st = INTERGROWTH-21st growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S6.4. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in INTERGROWTH-21<sup>st</sup> – UK**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 0.0%        | 97.9%       | 0.0%  | 95.8% | 0.49 (0.26-0.73) |
| SGA                                      | 0.0%        | 92.1%       | 0.0%  | 95.6% | 0.46 (0.24-0.68) |
| BW <10 <sup>th</sup> MGRS                | 0.0%        | 92.9%       | 0.0%  | 95.6% | 0.47 (0.25-0.69) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.0%        | 95.7%       | 0.0%  | 95.7% | 0.48 (0.25-0.71) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 0.0%        | 96.4%       | 0.0%  | 95.7% | 0.48 (0.25-0.71) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.0%        | 94.9%       | 0.0%  | 95.6% | 0.48 (0.25-0.70) |
| HC <10 <sup>th</sup> MGRS                | 0.0%        | 93.5%       | 0.0%  | 95.6% | 0.47 (0.25-0.70) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 16.7%       | 95.0%       | 12.5% | 96.4% | 0.56 (0.31-0.82) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 0.0%        | 97.1%       | 0.0%  | 95.7% | 0.49 (0.26-0.72) |
| PI-for-age <10 <sup>th</sup> percentile  | 0.0%        | 94.9%       | 0.0%  | 95.6% | 0.48 (0.25-0.70) |
| BMI <10 <sup>th</sup> percentile         | 0.0%        | 98.6%       | 0.0%  | 95.8% | 0.49 (0.26-0.73) |
| BMI-for-age <10 <sup>th</sup> percentile | 0.0%        | 96.4%       | 0.0%  | 95.7% | 0.48 (0.25-0.71) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 0.0%        | 94.9%       | 0.0%  | 95.6% | 0.48 (0.25-0.70) |
| HC/PI >90 <sup>th</sup> percentile       | 0.0%        | 95.7%       | 0.0%  | 95.7% | 0.48 (0.25-0.71) |
| HC/BMI >90 <sup>th</sup> percentile      | 0.0%        | 97.8%       | 0.0%  | 95.7% | 0.49 (0.26-0.72) |

**Table S6.5. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in INTERGROWTH-21<sup>st</sup> – Italy**

| Variables                                | Sensitivity | Specificity | PPV   | NPV    | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|--------|------------------|
| <b>Birth weight indices</b>              |             |             |       |        |                  |
| BW <2500g                                | 0.0%        | 96.1%       | 0.0%  | 99.5%  | 0.49 (0.00-1.00) |
| SGA                                      | 100.0%      | 81.6%       | 2.6%  | 100.0% | 0.91 (0.80-1.00) |
| BW <10 <sup>th</sup> MGRS                | 0.0%        | 87.7%       | 0.0%  | 99.4%  | 0.44 (0.00-0.94) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 100.0%      | 88.7%       | 4.2%  | 100.0% | 0.95 (0.88-1.00) |
| <b>Stunting indices</b>                  |             |             |       |        |                  |
| BL < 10 <sup>th</sup> MGRS               | 0.0%        | 98.7%       | 0.0%  | 99.5%  | 0.45 (0.00-0.97) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 100.0%      | 93.5%       | 7.1%  | 100.0% | 0.97 (0.92-1.00) |
| HC <10 <sup>th</sup> MGRS                | 100.0%      | 92.0%       | 5.9%  | 100.0% | 0.97 (0.92-1.00) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 100.0%      | 97.5%       | 16.7% | 100.0% | 0.99 (0.97-1.00) |
| <b>Wasting indices</b>                   |             |             |       |        |                  |
| PI <10 <sup>th</sup> percentile          | 0.0%        | 93.1%       | 0.0%  | 99.5%  | 0.47 (0.00-1.00) |
| PI-for-age <10 <sup>th</sup> percentile  | 0.0%        | 92.5%       | 0.0%  | 99.5%  | 0.46 (0.00-0.99) |
| BMI <10 <sup>th</sup> percentile         | 0.0%        | 93.6%       | 0.0%  | 99.5%  | 0.47 (0.00-1.00) |
| BMI-for-age <10 <sup>th</sup> percentile | 0.0%        | 91.5%       | 0.0%  | 99.5%  | 0.46 (0.00-0.98) |
| <b>Asymmetry indices</b>                 |             |             |       |        |                  |
| HC/BL >90 <sup>th</sup> percentile       | 0.0%        | 89.6%       | 0.0%  | 99.4%  | 0.45 (0.00-0.96) |
| HC/PI >90 <sup>th</sup> percentile       | 0.0%        | 93.0%       | 0.0%  | 99.5%  | 0.47 (0.00-1.00) |
| HC/BMI >90 <sup>th</sup> percentile      | 0.0%        | 93.0%       | 0.0%  | 99.5%  | 0.47 (0.00-1.00) |

**Table S6.6. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in INTERGROWTH-21<sup>st</sup> – Brazil**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 0.0%        | 95.4%       | 0.0%  | 96.3% | 0.48 (0.20-0.75) |
| SGA                                      | 0.0%        | 86.2%       | 0.0%  | 95.9% | 0.43 (0.18-0.68) |
| BW <10 <sup>th</sup> MGRS                | 0.0%        | 88.1%       | 0.0%  | 96.0% | 0.44 (0.18-0.70) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.0%        | 92.7%       | 0.0%  | 96.2% | 0.46 (0.19-0.73) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 25.0%       | 79.8%       | 4.3%  | 96.7% | 0.52 (0.23-0.82) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 25.0%       | 89.9%       | 8.3%  | 97.0% | 0.58 (0.26-0.89) |
| HC <10 <sup>th</sup> MGRS                | 25.0%       | 91.7%       | 10.0% | 97.1% | 0.58 (0.27-0.90) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.0%        | 97.2%       | 0.0%  | 96.4% | 0.49 (0.20-0.77) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 0.0%        | 99.1%       | 0.0%  | 96.4% | 0.50 (0.21-0.78) |
| PI-for-age <10 <sup>th</sup> percentile  | 0.0%        | 98.2%       | 0.0%  | 96.4% | 0.49 (0.21-0.78) |
| BMI <10 <sup>th</sup> percentile         | 0.0%        | 96.3%       | 0.0%  | 96.3% | 0.48 (0.20-0.76) |
| BMI-for-age <10 <sup>th</sup> percentile | 0.0%        | 97.2%       | 0.0%  | 96.4% | 0.49 (0.20-0.77) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 25.0%       | 81.7%       | 4.8%  | 96.7% | 0.53 (0.24-0.83) |
| HC/PI >90 <sup>th</sup> percentile       | 0.0%        | 98.2%       | 0.0%  | 96.4% | 0.49 (0.21-0.78) |
| HC/BMI >90 <sup>th</sup> percentile      | 0.0%        | 97.2%       | 0.0%  | 96.4% | 0.49 (0.20-0.77) |



**Table S6.7. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in INTERGROWTH-21<sup>st</sup> – India**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 0.0%        | 88.4%       | 0.0%  | 87.7% | 0.44 (0.34-0.54) |
| SGA                                      | 30.0%       | 59.8%       | 8.5%  | 87.3% | 0.45 (0.34-0.56) |
| BW <10 <sup>th</sup> MGRS                | 36.7%       | 62.2%       | 10.8% | 88.8% | 50 (0.39-0.60)   |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 20.0%       | 78.8%       | 10.5% | 88.8% | 0.49 (0.39-0.60) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 13.3%       | 80.5%       | 7.8%  | 88.2% | 0.47 (0.39-0.58) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 13.3%       | 90.0%       | 14.3% | 89.3% | 0.52 (0.41-0.63) |
| HC <10 <sup>th</sup> MGRS                | 20.0%       | 67.6%       | 7.1%  | 87.2% | 0.44 (0.33-0.54) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 16.7%       | 85.1%       | 12.2% | 89.1% | 0.51 (0.40-0.57) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 16.7%       | 76.3%       | 8.1%  | 88.0% | 0.47 (0.36-0.57) |
| PI-for-age <10 <sup>th</sup> percentile  | 23.3%       | 78.8%       | 12.1% | 89.2% | 0.51 (0.40-0.62) |
| BMI <10 <sup>th</sup> percentile         | 10.0%       | 76.3%       | 5.0%  | 87.2% | 0.43 (0.33-0.53) |
| BMI-for-age <10 <sup>th</sup> percentile | 20.0%       | 79.3%       | 10.7% | 88.8% | 0.49 (0.39-0.61) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 0.0%        | 97.1%       | 0.0%  | 88.6% | 0.49 (0.38-0.59) |
| HC/PI >90 <sup>th</sup> percentile       | 16.7%       | 79.3%       | 9.1%  | 88.4% | 0.48 (0.37-0.59) |
| HC/BMI >90 <sup>th</sup> percentile      | 13.3%       | 78.8%       | 7.2%  | 88.0% | 0.46 (0.36-0.57) |

**Table S6.8. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in INTERGROWTH-21<sup>st</sup> – Kenya**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 5.3%        | 93.2%       | 4.3%  | 94.4% | 0.47 (0.34-0.60) |
| SGA                                      | 11.1%       | 91.9%       | 3.3%  | 94.3% | 0.46 (0.33-0.60) |
| BW <10 <sup>th</sup> MGRS                | 36.7%       | 62.2%       | 10.8% | 88.8% | 0.50 (0.39-0.60) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 5.3%        | 89.8%       | 2.9%  | 94.2% | 0.48 (0.34-0.61) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 21.1%       | 86.6%       | 8.5%  | 94.9% | 0.52 (0.38-0.66) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 22.2%       | 87.1%       | 8.9%  | 95.2% | 0.55 (0.40-0.69) |
| HC <10 <sup>th</sup> MGRS                | 5.3%        | 90.6%       | 3.2%  | 94.2% | 0.46 (0.33-0.58) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.0%        | 94.3%       | 0.0%  | 94.3% | 0.47 (0.34-0.60) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 5.3%        | 91.9%       | 3.7%  | 94.2% | 0.46 (0.33-0.58) |
| PI-for-age <10 <sup>th</sup> percentile  | 0.0%        | 92.8%       | 0.0%  | 94.2% | 0.46 (0.34-0.59) |
| BMI <10 <sup>th</sup> percentile         | 5.3%        | 91.2%       | 3.4%  | 94.2% | 0.46 (0.33-0.59) |
| BMI-for-age <10 <sup>th</sup> percentile | 0.0%        | 90.6%       | 0.0%  | 94.1% | 0.45 (0.33-0.58) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 0.0%        | 97.1%       | 0.0%  | 88.6% | 0.49 (0.38-0.59) |
| HC/PI >90 <sup>th</sup> percentile       | 16.7%       | 79.3%       | 9.1%  | 88.4% | 0.48 (0.37-0.59) |
| HC/BMI >90 <sup>th</sup> percentile      | 13.3%       | 78.8%       | 7.3%  | 88.0% | 0.46 (0.36-0.57) |

**Table S6.9. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in INTERGROWTH-21<sup>st</sup> – UK**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 0.0%        | 95.6%       | 0.0%  | 79.1% | 0.49 (0.38-0.59) |
| SGA                                      | 2.9%        | 91.1%       | 7.7%  | 78.8% | 0.47 (0.36-0.58) |
| BW <10 <sup>th</sup> MGRS                | 2.9%        | 90.4%       | 7.1%  | 78.7% | 0.47 (0.37-0.58) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 2.9%        | 95.6%       | 14.3% | 79.6% | 0.49 (0.38-0.60) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 2.9%        | 93.9%       | 11.1% | 79.0% | 0.48 (0.38-0.59) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 5.9%        | 94.7%       | 22.2% | 79.6% | 0.50 (0.39-0.61) |
| HC <10 <sup>th</sup> MGRS                | 8.8%        | 91.8%       | 21.4% | 79.9% | 0.51 (0.40-0.62) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 8.8%        | 95.5%       | 33.3% | 80.5% | 0.53 (0.42-0.64) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 0.0%        | 96.2%       | 0.0%  | 78.9% | 0.48 (0.37-0.59) |
| PI-for-age <10 <sup>th</sup> percentile  | 8.8%        | 96.2%       | 37.5% | 80.4% | 0.53 (0.41-0.64) |
| BMI <10 <sup>th</sup> percentile         | 0.0%        | 97.7%       | 0.0%  | 79.1% | 0.49 (0.38-0.60) |
| BMI-for-age <10 <sup>th</sup> percentile | 3.6%        | 96.2%       | 16.7% | 79.4% | 0.50 (0.39-0.60) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 11.8%       | 93.9%       | 33.3% | 80.5% | 0.53 (0.42-0.64) |
| HC/PI >90 <sup>th</sup> percentile       | 5.9%        | 96.2%       | 28.6% | 79.9% | 0.51 (0.40-0.62) |
| HC/BMI >90 <sup>th</sup> percentile      | 2.9%        | 97.7%       | 25.0% | 79.6% | 0.50 (0.39-0.61) |

**Table S6.10. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in INTERGROWTH-21<sup>st</sup> – Italy**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 2.8%        | 95.3%       | 12.5% | 80.2% | 0.49 (0.39-0.60) |
| SGA                                      | 13.9%       | 79.1%       | 13.9% | 79.1% | 0.46 (0.36-0.57) |
| BW <10 <sup>th</sup> MGRS                | 8.3%        | 85.9%       | 12.5% | 79.5% | 0.47 (0.37-0.57) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 8.3%        | 86.6%       | 13.0% | 79.6% | 0.48 (0.37-0.58) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 8.3%        | 87.9%       | 14.3% | 79.9% | 0.48 (0.38-0.59) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 8.3%        | 91.2%       | 18.8% | 80.4% | 0.50 (0.39-0.60) |
| HC <10 <sup>th</sup> MGRS                | 5.6%        | 90.5%       | 12.5% | 79.6% | 0.48 (0.38-0.59) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.0%        | 97.3%       | 0.0%  | 79.8% | 0.49 (0.38-0.59) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 11.1%       | 94.6%       | 33.3% | 81.5% | 0.53 (0.42-0.64) |
| PI-for-age <10 <sup>th</sup> percentile  | 11.1%       | 92.6%       | 26.7% | 81.8% | 0.52 (0.41-0.63) |
| BMI <10 <sup>th</sup> percentile         | 8.3%        | 94.0%       | 25.0% | 80.9% | 0.51 (0.41-0.62) |
| BMI-for-age <10 <sup>th</sup> percentile | 8.3%        | 90.5%       | 17.6% | 80.2% | 0.49 (0.39-0.60) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 8.3%        | 86.4%       | 13.0% | 79.4% | 0.47 (0.37-0.58) |
| HC/PI >90 <sup>th</sup> percentile       | 13.9%       | 93.9%       | 35.7% | 81.7% | 0.54 (0.43-0.65) |
| HC/BMI >90 <sup>th</sup> percentile      | 11.1%       | 93.9%       | 30.8% | 81.2% | 0.53 (0.42-0.63) |

**Table S6.11. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in INTERGROWTH-21<sup>st</sup> – Brazil**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 0.0%        | 94.8%       | 0.0%  | 85.2% | 0.47 (0.33-0.62) |
| SGA                                      | 0.0%        | 84.5%       | 0.0%  | 83.7% | 0.42 (0.29-0.56) |
| BW <10 <sup>th</sup> MGRS                | 6.2%        | 87.6%       | 7.7%  | 85.0% | 0.47 (0.32-0.62) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.0%        | 91.8%       | 0.0%  | 84.8% | 0.46 (0.31-0.60) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 25.0%       | 80.4%       | 17.4% | 86.7% | 0.52 (0.37-0.68) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 6.2%        | 88.7%       | 8.3%  | 85.1% | 0.48 (0.33-0.62) |
| HC <10 <sup>th</sup> MGRS                | 18.8%       | 92.8%       | 30.0% | 87.4% | 0.56 (0.40-0.72) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.0%        | 96.9%       | 0.0%  | 85.5% | 0.49 (0.34-0.64) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 0.0%        | 99.0%       | 0.0%  | 85.7% | 0.50 (0.34-0.65) |
| PI-for-age <10 <sup>th</sup> percentile  | 0.0%        | 97.8%       | 0.0%  | 85.6% | 0.49 (0.34-0.64) |
| BMI <10 <sup>th</sup> percentile         | 0.0%        | 95.9%       | 0.0%  | 85.3% | 0.48 (0.33-0.63) |
| BMI-for-age <10 <sup>th</sup> percentile | 0.0%        | 96.9%       | 0.0%  | 85.5% | 0.49 (0.34-0.64) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 18.8%       | 81.4%       | 14.3% | 85.9% | 0.50 (0.35-0.65) |
| HC/PI >90 <sup>th</sup> percentile       | 6.2%        | 99.0%       | 50.0% | 86.5% | 0.53 (0.37-0.68) |
| HC/BMI >90 <sup>th</sup> percentile      | 0.0%        | 96.9%       | 0.0%  | 85.5% | 0.49 (0.34-0.64) |

**Table S6.12. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in INTERGROWTH-21<sup>st</sup> – India**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 12.3%       | 90.4%       | 33.3% | 72.6% | 0.51 (0.44-0.59) |
| SGA                                      | 42.5%       | 64.4%       | 31.6% | 74.2% | 0.53 (0.46-0.61) |
| BW <10 <sup>th</sup> MGRS                | 43.8%       | 66.5%       | 33.7% | 75.3% | 0.55 (0.47-0.63) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 30.1%       | 81.9%       | 39.3% | 75.1% | 0.56 (0.48-0.64) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 13.7%       | 78.2%       | 19.6% | 70.0% | 0.46 (0.38-0.54) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 11.0%       | 89.4%       | 28.6% | 72.1% | 0.50 (0.42-0.58) |
| HC <10 <sup>th</sup> MGRS                | 32.9%       | 70.7%       | 30.4% | 73.1% | 0.52 (0.44-0.60) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 16.4%       | 86.2%       | 31.6% | 72.6% | 0.51 (0.43-0.59) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 32.9%       | 82.4%       | 42.1% | 76.0% | 0.58 (0.50-0.66) |
| PI-for-age <10 <sup>th</sup> percentile  | 27.4%       | 81.9%       | 37.0% | 74.4% | 0.55 (0.47-0.63) |
| BMI <10 <sup>th</sup> percentile         | 30.1%       | 82.4%       | 40.0% | 75.2% | 0.56 (0.48-0.64) |
| BMI-for-age <10 <sup>th</sup> percentile | 26.0%       | 83.0%       | 37.3% | 74.3% | 0.55 (0.47-0.63) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 2.7%        | 96.8%       | 25.0% | 71.9% | 0.50 (0.42-0.58) |
| HC/PI >90 <sup>th</sup> percentile       | 24.7%       | 84.6%       | 38.3% | 74.3% | 0.55 (0.47-0.63) |
| HC/BMI >90 <sup>th</sup> percentile      | 26.0%       | 84.0%       | 38.8% | 74.5% | 0.55 (0.47-0.63) |

**Table S6.13. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in INTERGROWTH-21<sup>st</sup> – Kenya**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 7.0%        | 93.3%       | 21.7% | 79.0% | 0.49 (0.41-0.57) |
| SGA                                      | 14.5%       | 81.2%       | 16.7% | 78.5% | 0.48 (0.40-0.56) |
| BW <10 <sup>th</sup> MGRS                | 43.8%       | 66.5%       | 33.7% | 75.3% | 0.55 (0.47-0.63) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 7.0%        | 89.1%       | 14.7% | 78.3% | 0.48 (0.41-0.56) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 10.0%       | 85.3%       | 15.2% | 78.2% | 0.47 (0.40-0.55) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 8.8%        | 85.6%       | 13.6% | 78.5% | 0.51 (0.43-0.59) |
| HC <10 <sup>th</sup> MGRS                | 12.9%       | 91.7%       | 29.0% | 79.9% | 0.50 (0.43-0.58) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 5.9%        | 94.7%       | 22.2% | 79.6% | 0.48 (0.41-0.56) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 5.7%        | 92.1%       | 16.0% | 78.7% | 0.49 (0.41-0.56) |
| PI-for-age <10 <sup>th</sup> percentile  | 4.4%        | 93.2%       | 14.3% | 79.1% | 0.49 (0.41-0.56) |
| BMI <10 <sup>th</sup> percentile         | 10.0%       | 91.7%       | 24.1% | 79.4% | 0.50 (0.42-0.57) |
| BMI-for-age <10 <sup>th</sup> percentile | 7.4%        | 90.9%       | 17.2% | 79.2% | 0.49 (0.42-0.57) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 2.7%        | 96.8%       | 25.0% | 71.9% | 0.50 (0.42-0.58) |
| HC/PI >90 <sup>th</sup> percentile       | 24.7%       | 84.6%       | 38.3% | 74.3% | 0.55 (0.47-0.63) |
| HC/BMI >90 <sup>th</sup> percentile      | 26.0%       | 84.0%       | 38.8% | 74.5% | 0.55 (0.47-0.63) |

**Table S6.14. Descriptive statistics (*M*, *SD*), frequencies (*n*, %), ANOVA and chi-squared analyses comparing INTERGROWTH-21<sup>st</sup> UK and Brazil sites with the ALSPAC and Pelotas cohorts, respectively**

| Variables                        | I-21 <sup>st</sup> UK<br>(N=174) | ALSPAC<br>(N=7829) | F/ $\chi^2$ | <i>p</i> | I-21 <sup>st</sup> Brazil<br>(N=113) | Pelotas 2004<br>(N=3749) | F/ $\chi^2$ | <i>p</i> |
|----------------------------------|----------------------------------|--------------------|-------------|----------|--------------------------------------|--------------------------|-------------|----------|
| Maternal school (years)          | 16.26 (2.99)                     | 10.79 (1.95)       | 1328.54     | <.001**  | 13.86 (3.21)                         | 8.13 (3.45)              | 303.85      | <.001**  |
| Maternal age at delivery (years) | 30.59 (3.24)                     | 27.96 (4.98)       | 48.01       | <.001**  | 28.75 (4.02)                         | 26.19 (6.84)             | 15.69       | <.001**  |
| Maternal BMI                     | 23.41 (2.74)                     | 22.94 (3.84)       | 2.65        | .104     | 24.03 (2.86)                         | 24.68 (4.58)             | 2.22        | .137     |
| Preterm delivery (<37 weeks)     | 5 (2.9%)                         | 347 (4.4%)         | 1.69        | .290     | 6 (5.3%)                             | 515 (13.8%)              | 6.69        | .007*    |
| Cesarean section                 | 28 (16.1%)                       | 747 (9.9%)         | 942.14      | <.001**  | 97 (85.8%)                           | 1702 (45.4%)             | 72.10       | <.001**  |
| Child sex (male)                 | 91 (52.3%)                       | 4020 (51.4%)       | 0.04        | .878     | 60 (53.1%)                           | 1943 (51.8%)             | 0.07        | .849     |
| APGAR score <7                   | 1 (0.6%)                         | 45 (1.0%)          | 0.86        | .522     | 1 (0.9%)                             | 61 (1.6%)                | 0.38        | .450     |
| Breastfeed <6 months             | 55 (31.6%)                       | 5890 (64.5%)       | 87.70       | <.001**  | 28 (24.8%)                           | 1854 (49.6%)             | 26.93       | <.001**  |
| Birth weight (g)                 | 3457 (523)                       | 3443 (527)         | 1.07        | .301     | 3231 (473)                           | 3171 (531)               | 1.41        | .235     |
| Birth length (cm)                | 50.00 (1.99)                     | 50.68 (2.43)       | 13.18       | <.001**  | 48.51 (2.26)                         | 48.21 (2.51)             | 1.57        | .210     |
| Head circumference (cm)          | 34.40 (1.51)                     | 34.83 (1.49)       | 11.99       | .001*    | 34.01 (1.55)                         | 34.00 (1.63)             | 0.01        | .933     |
| Ponderal index                   | 2.77 (0.22)                      | 2.62 (0.29)        | 30.25       | <.001**  | 2.81 (0.24)                          | 2.81 (0.29)              | 0.00        | .954     |
| Body mass index                  | 13.85 (1.21)                     | 13.32 (1.37)       | 23.50       | <.001**  | 13.65 (1.31)                         | 13.56 (1.46)             | 0.46        | .497     |
| Attention score                  | 2.91 (1.72)                      | 3.38 (2.37)        | 5.67        | .017*    | 2.93 (1.78)                          | 2.62 (2.33)              | 2.00        | .158     |
| Cognitive score                  | -0.03 (0.88)                     | 0.00 (1.00)        | 0.12        | .733     | 0.63 (0.44)                          | 0.00 (1.00)              | 44.59       | <.001**  |

\* =  $p < .05$ ; \*\* =  $p < .001$



## Chapter 7

**Table S7.1. Descriptive statistics (*M*, *SD*), frequencies (*n*, %), ANOVA and chi-squared analyses comparing males and females on maternal and child characteristics**

| Variable                         | Pelotas (N=3508) |              |             | ALSPAC (N=6768) |              |             | INTERGROWTH-21 <sup>st</sup> (N=1126) |              |             |
|----------------------------------|------------------|--------------|-------------|-----------------|--------------|-------------|---------------------------------------|--------------|-------------|
|                                  | Males            | Females      | F/ $\chi^2$ | Males           | Females      | F/ $\chi^2$ | Males                                 | Females      | F/ $\chi^2$ |
| Maternal school (years)          | 8.21 (3.46)      | 8.04 (3.44)  | 2.41        | 10.77 (1.94)    | 10.81 (1.96) | 1.31        | 15.30 (2.68)                          | 15.28 (2.75) | 0.02        |
| Maternal age at delivery (years) | 26.14 (6.83)     | 26.24 (6.85) | 0.19        | 28.07 (5.02)    | 27.85 (4.94) | 6.42*       | 28.85 (3.90)                          | 28.80 (3.85) | 0.05        |
| Maternal BMI                     | 24.62 (4.51)     | 24.74 (4.67) | 0.41        | 22.97 (3.84)    | 22.89 (3.83) | 1.08        | 23.36 (3.07)                          | 23.20 (2.97) | 0.79        |
| Smoked during pregnancy          | 522 (26.9%)      | 496 (27.5%)  | 0.17        | 1713 (26.1%)    | 1500 (24.3%) | 5.84*       | 0 (0.0%)                              | 0 (0.0%)     | 0.00        |
| Alcohol during pregnancy         | 67 (3.4%)        | 58 (3.2%)    | 0.16        | 4066 (63.5%)    | 3815 (63.4%) | 0.02        | 0 (0.0%)                              | 0 (0.0%)     | 0.00        |
| Preterm delivery (<37 weeks)     | 260 (13.4%)      | 255 (14.1%)  | 0.43        | 395 (5.6%)      | 291 (4.4%)   | 10.42*      | 10 (1.8%)                             | 36 (6.3%)    | 14.70**     |
| Cesarean section                 | 910 (46.8%)      | 792 (43.9%)  | 3.36        | 610 (10.3%)     | 545 (9.8%)   | 0.80        | 228 (40.9%)                           | 216 (38.0%)  | 0.99        |
| APGAR score <7                   | 38 (2.0%)        | 23 (1.3%)    | 2.70        | 69 (1.7%)       | 43 (1.1%)    | 4.82*       | 4 (0.7%)                              | 0 (0.0%)     | 4.09*       |
| Breastfeed <6 months             | 983 (50.7%)      | 871 (48.3%)  | 2.13        | 3687 (67.0%)    | 3321 (64.4%) | 7.86*       | 94 (16.9%)                            | 86 (15.1%)   | 0.65        |
| Birth weight (g)                 | 3224 (536)       | 3115 (520)   | 39.63**     | 3468 (561)      | 3357 (512)   | 141.10**    | 3280 (492)                            | 3089 (492)   | 42.13**     |
| Birth length (cm)                | 48.57 (2.51)     | 47.83 (2.46) | 81.46**     | 51.05 (2.44)    | 50.28 (2.35) | 258.07**    | 49.50 (2.08)                          | 48.62 (2.11) | 48.99**     |
| Head circumference (cm)          | 34.28 (1.59)     | 33.70 (1.62) | 122.57**    | 35.12 (1.52)    | 34.46 (1.40) | 518.23**    | 34.27 (1.42)                          | 33.56 (1.40) | 70.35**     |
| Ponderal index                   | 2.80 (0.28)      | 2.83 (0.30)  | 11.23*      | 2.62 (0.31)     | 2.65 (0.35)  | 27.78**     | 2.69 (0.26)                           | 2.68 (0.28)  | 1.11        |
| Body mass index                  | 13.58 (1.46)     | 13.53 (1.46) | 1.26        | 13.33 (1.43)    | 13.30 (1.46) | 1.49        | 13.32 (1.37)                          | 13.01 (1.42) | 14.28**     |
| Attention score                  | 2.82 (2.36)      | 2.40 (2.28)  | 31.52**     | 3.78 (2.46)     | 2.96 (2.19)  | 240.23**    | 3.04 (2.08)                           | 2.91 (1.99)  | 1.22        |
| Cognitive score                  | -0.10 (1.01)     | 0.11 (0.97)  | 44.68**     | -0.08 (1.01)    | 0.09 (0.99)  | 6.94*       | -0.11 (1.01)                          | 0.11 (0.97)  | 13.31**     |

\* =  $p < .05$ ; \*\* =  $p < .001$

**Table S7.2. Unadjusted associations (*OR*) between indices of fetal growth and attention impairment in males and females by site**

| Variable                                 | Males |       |        |       |       | Females |       |        |       |       |
|------------------------------------------|-------|-------|--------|-------|-------|---------|-------|--------|-------|-------|
|                                          | UK    | Italy | Brazil | Kenya | India | UK      | Italy | Brazil | Kenya | India |
| <b>Birth weight indices</b>              |       |       |        |       |       |         |       |        |       |       |
| BW <2500g                                | 1.00  | 1.00  | 16.40  | 0.58  | 0.62  | 3.93    | 2.58  | 0.28   | 0.69  | 0.50  |
| SGA                                      | 0.15  | 0.82  | 0.66   | 0.57  | 0.62  | 5.90*   | 1.27  | 0.31   | 0.98  | 0.73  |
| BW <10 <sup>th</sup> MGRS                | 0.15  | 1.05  | 1.26   | 0.68  | 0.75  | 5.79*   | 1.00  | 0.42   | 0.64  | 0.93  |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.00  | 1.42  | 1.23   | 0.49  | 1.27  | 2.29    | 0.86  | 0.17*  | 0.65  | 0.58  |
| <b>Stunting indices</b>                  |       |       |        |       |       |         |       |        |       |       |
| BL < 10 <sup>th</sup> MGRS               | 0.38  | 1.57  | 1.27   | 0.50  | 0.92  | 19.34*  | 1.39  | 1.39   | 1.33  | 0.54  |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.08  | 0.64  | 1.72   | 0.69  | 1.91  | 5.32*   | 1.53  | 4.92*  | 2.46* | 0.72  |
| HC <10 <sup>th</sup> MGRS                | 0.25  | 1.37  | 5.89*  | 0.89  | 0.62  | 8.41*   | 2.75  | 1.33   | 0.71  | 0.56  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.09* | 1.06  | 16.35  | 0.97  | 0.96  | 4.68    | 1.00  | 1.91   | 0.94  | 0.42  |
| <b>Wasting indices</b>                   |       |       |        |       |       |         |       |        |       |       |
| PI <10 <sup>th</sup> percentile          | 1.00  | 0.98  | 1.00   | 1.23  | 0.67  | 1.56    | 0.91  | 8.23   | 0.52  | 0.98  |
| PI-for-age <10 <sup>th</sup> percentile  | 1.76  | 0.79  | 16.35  | 1.18  | 1.15  | 1.67    | 0.40  | 8.23   | 0.47  | 1.14  |
| BMI <10 <sup>th</sup> percentile         | 1.00  | 1.63  | 16.35  | 1.38  | 0.55  | 2.32    | 2.54  | 0.43   | 0.57  | 1.04  |
| BMI-for-age <10 <sup>th</sup> percentile | 0.16  | 0.80  | 16.35  | 1.07  | 0.99  | 2.57    | 0.79  | 1.81   | 0.67  | 1.32  |
| <b>Asymmetry indices</b>                 |       |       |        |       |       |         |       |        |       |       |
| HC/BL >90 <sup>th</sup> percentile       | 0.58  | 0.97  | 0.64   | 1.34  | 1.00  | 0.11    | 0.67  | 0.56   | 2.58* | 0.93  |
| HC/PI >90 <sup>th</sup> percentile       | 2.67  | 1.22  | 0.45   | 0.79  | 0.82  | 0.75    | 0.33  | 1.00   | 0.40* | 0.84  |
| HC/BMI >90 <sup>th</sup> percentile      | 1.20  | 0.81  | 0.63   | 0.97  | 0.67  | 2.32    | 0.48  | 0.11   | 0.56  | 0.95  |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21st = INTERGROWTH-21st growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S7.3. Unadjusted associations (OR) between indices of fetal growth and cognitive impairment in males and females by site**

| Variable                                 | Males |       |        |       |       | Females |       |        |       |       |
|------------------------------------------|-------|-------|--------|-------|-------|---------|-------|--------|-------|-------|
|                                          | UK    | Italy | Brazil | Kenya | India | UK      | Italy | Brazil | Kenya | India |
| <b>Birth weight indices</b>              |       |       |        |       |       |         |       |        |       |       |
| BW <2500g                                | 1.31  | 5.10  | 1.66   | 0.38  | 1.65  | 0.64    | 0.59  | 0.79   | 0.51  | 1.06  |
| SGA                                      | 0.14* | 2.04  | 0.30   | 0.79  | 1.38  | 1.55    | 0.47  | 0.71   | 0.97  | 1.05  |
| BW <10 <sup>th</sup> MGRS                | 0.15  | 1.89  | 0.41   | 0.55  | 1.65  | 1.21    | 0.43  | 2.38   | 0.43* | 1.32  |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.67  | 3.11  | 0.27   | 0.42  | 2.79* | 3.42    | 0.36  | 1.17   | 0.89  | 1.09  |
| <b>Stunting indices</b>                  |       |       |        |       |       |         |       |        |       |       |
| BL < 10 <sup>th</sup> MGRS               | 0.27  | 1.54  | 1.20   | 0.76  | 0.33  | 0.63    | 0.41  | 1.06   | 0.72  | 0.78  |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.79  | 1.24  | 0.70   | 0.52  | 0.34  | 0.73    | 0.82  | 0.41   | 1.32  | 1.04  |
| HC <10 <sup>th</sup> MGRS                | 0.36  | 0.99  | 4.19   | 0.64  | 0.95  | 1.03    | 0.55  | 8.79*  | 0.50  | 1.45  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 0.46  | 0.31  | 1.66   | 0.14  | 1.29  | 2.89    | 1.49  | 5.41   | 0.81  | 1.15  |
| <b>Wasting indices</b>                   |       |       |        |       |       |         |       |        |       |       |
| PI <10 <sup>th</sup> percentile          | 1.00  | 4.91* | 1.00   | 0.49  | 2.31* | 0.54    | 0.36  | 6.92   | 0.46  | 1.83  |
| PI-for-age <10 <sup>th</sup> percentile  | 3.01  | 3.89  | 1.66   | 0.36  | 2.11  | 1.21    | 0.16  | 6.92   | 0.95  | 1.68  |
| BMI <10 <sup>th</sup> percentile         | 1.00  | 5.99* | 1.66   | 0.62  | 1.81  | 0.73    | 0.90  | 2.35   | 0.78  | 2.30* |
| BMI-for-age <10 <sup>th</sup> percentile | 1.52  | 2.33  | 1.66   | 0.43  | 1.78  | 1.11    | 0.35  | 5.90   | 0.90  | 1.68  |
| <b>Asymmetry indices</b>                 |       |       |        |       |       |         |       |        |       |       |
| HC/BL >90 <sup>th</sup> percentile       | 2.44  | 0.91  | 1.06   | 1.27  | 0.99  | 1.35    | 0.70  | 0.19   | 0.86  | 0.99  |
| HC/PI >90 <sup>th</sup> percentile       | 3.12  | 5.80* | 2.12   | 0.79  | 1.62  | 0.68    | 0.13  | 1.00   | 1.04  | 1.47  |
| HC/BMI >90 <sup>th</sup> percentile      | 8.42  | 7.64* | 1.00   | 0.57  | 2.49* | 0.73    | 0.38  | 0.99   | 0.49  | 0.96  |

BL=birth length; BMI=body mass index; BW=birth weight; HC=head circumference; I-21st = INTERGROWTH-21st growth standards; MGRS=multicenter growth reference study growth standards; PI=ponderal index; SGA=small-for-gestational-age; \* = p<.05; \*\*=p<.001

**Table S7.4. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in Pelotas in males**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 9.4%        | 92.2%       | 9.7%  | 92.0% | 0.51 (0.46-0.55) |
| SGA                                      | 20.9%       | 85.1%       | 11.1% | 92.4% | 0.52 (0.48-0.57) |
| BW <10 <sup>th</sup> MGRS                | 20.8%       | 82.2%       | 9.4%  | 92.1% | 0.51 (0.46-0.56) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 15.3%       | 90.8%       | 12.8% | 92.4% | 0.53 (0.48-0.58) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 33.1%       | 72.0%       | 9.5%  | 92.4% | 0.52 (0.48-0.57) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 22.4%       | 82.2%       | 10.0% | 92.3% | 0.52 (0.48-0.57) |
| HC <10 <sup>th</sup> MGRS                | 18.5%       | 86.3%       | 10.7% | 92.3% | 0.48 (0.43-0.53) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 6.4%        | 93.2%       | 7.6%  | 91.9% | 0.50 (0.45-0.55) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 12.1%       | 90.2%       | 9.8%  | 92.1% | 0.51 (0.46-0.56) |
| PI-for-age <10 <sup>th</sup> percentile  | 9.0%        | 90.2%       | 7.4%  | 91.9% | 0.51 (0.46-0.55) |
| BMI <10 <sup>th</sup> percentile         | 12.1%       | 90.2%       | 9.8%  | 92.1% | 0.52 (0.47-0.57) |
| BMI-for-age <10 <sup>th</sup> percentile | 10.9%       | 90.3%       | 9.0%  | 92.0% | 0.51 (0.46-0.55) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 14.0%       | 89.1%       | 10.2% | 92.1% | 0.52 (0.47-0.56) |
| HC/PI >90 <sup>th</sup> percentile       | 12.7%       | 87.3%       | 9.2%  | 91.9% | 0.50 (0.45-0.55) |
| HC/BMI >90 <sup>th</sup> percentile      | 14.0%       | 89.2%       | 10.3% | 92.2% | 0.51 (0.47-0.56) |

**Table S7.5. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in Pelotas in females**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)      |
|------------------------------------------|-------------|-------------|-------|-------|-------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                   |
| BW <2500g                                | 20.2%       | 90.4%       | 12.4% | 94.4% | 0.55 (0.50-0.61)  |
| SGA                                      | 26.3%       | 86.7%       | 11.8% | 94.6% | 0.57 (0.51-0.62)* |
| BW <10 <sup>th</sup> MGRS                | 32.5%       | 81.9%       | 10.8% | 94.7% | 0.57 (0.52-0.63)* |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 21.1%       | 91.2%       | 14.0% | 94.5% | 0.56 (0.50-0.62)* |
| <b>Stunting indices</b>                  |             |             |       |       |                   |
| BL < 10 <sup>th</sup> MGRS               | 41.2%       | 72.6%       | 9.3%  | 94.8% | 0.57 (0.51-0.63)* |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 33.3%       | 81.5%       | 10.9% | 94.8% | 0.58 (0.52-0.63)* |
| HC <10 <sup>th</sup> MGRS                | 28.1%       | 82.1%       | 9.6%  | 94.4% | 0.45 (0.39-0.51)  |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 12.3%       | 92.2%       | 9.7%  | 93.9% | 0.52 (0.47-0.58)  |
| <b>Wasting indices</b>                   |             |             |       |       |                   |
| PI <10 <sup>th</sup> percentile          | 15.8%       | 90.4%       | 10.0% | 94.1% | 0.53 (0.47-0.59)  |
| PI-for-age <10 <sup>th</sup> percentile  | 16.7%       | 90.7%       | 10.9% | 94.1% | 0.54 (0.48-0.59)  |
| BMI <10 <sup>th</sup> percentile         | 18.4%       | 90.6%       | 11.7% | 94.3% | 0.55 (0.49-0.60)  |
| BMI-for-age <10 <sup>th</sup> percentile | 13.2%       | 90.5%       | 8.6%  | 93.9% | 0.52 (0.46-0.58)  |
| <b>Asymmetry indices</b>                 |             |             |       |       |                   |
| HC/BL >90 <sup>th</sup> percentile       | 12.3%       | 91.6%       | 9.0%  | 93.9% | 0.52 (0.46-0.58)  |
| HC/PI >90 <sup>th</sup> percentile       | 9.6%        | 93.0%       | 8.6%  | 93.8% | 0.51 (0.46-0.57)  |
| HC/BMI >90 <sup>th</sup> percentile      | 12.3%       | 91.4%       | 8.8%  | 93.9% | 0.52 (0.46-0.58)  |

**Table S7.6. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in ALSPAC in males**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 4.4%        | 96.7%       | 18.1% | 85.9% | 0.51 (0.48-0.54) |
| SGA                                      | 10.0%       | 92.3%       | 17.9% | 86.0% | 0.51 (0.48-0.54) |
| BW <10 <sup>th</sup> MGRS                | 12.1%       | 91.1%       | 18.5% | 86.1% | 0.52 (0.49-0.55) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 6.2%        | 95.1%       | 17.3% | 85.9% | 0.51 (0.48-0.53) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 9.1%        | 94.1%       | 20.6% | 86.1% | 0.51 (0.49-0.54) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 6.0%        | 96.8%       | 23.7% | 86.0% | 0.51 (0.48-0.54) |
| HC <10 <sup>th</sup> MGRS                | 6.6%        | 95.4%       | 19.2% | 86.0% | 0.51 (0.48-0.54) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 1.8%        | 98.0%       | 12.9% | 85.7% | 0.50 (0.47-0.53) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 13.0%       | 89.9%       | 17.7% | 86.1% | 0.53 (0.49-0.54) |
| PI-for-age <10 <sup>th</sup> percentile  | 11.2%       | 90.5%       | 16.4% | 85.9% | 0.51 (0.48-0.54) |
| BMI <10 <sup>th</sup> percentile         | 12.3%       | 90.8%       | 18.3% | 86.1% | 0.52 (0.49-0.55) |
| BMI-for-age <10 <sup>th</sup> percentile | 12.8%       | 91.1%       | 19.3% | 86.2% | 0.52 (0.49-0.55) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 11.7%       | 90.1%       | 16.5% | 85.9% | 0.51 (0.48-0.54) |
| HC/PI >90 <sup>th</sup> percentile       | 11.0%       | 87.4%       | 12.7% | 85.5% | 0.49 (0.46-0.52) |
| HC/BMI >90 <sup>th</sup> percentile      | 13.0%       | 89.1%       | 16.6% | 86.0% | 0.51 (0.48-0.54) |

**Table S7.7. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in ALSPAC in females**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 6.1%        | 96.5%       | 12.1% | 92.8% | 0.51 (0.47-0.55) |
| SGA                                      | 11.8%       | 93.2%       | 12.2% | 92.9% | 0.53 (0.49-0.57) |
| BW <10 <sup>th</sup> MGRS                | 12.2%       | 93.1%       | 12.5% | 93.0% | 0.52 (0.48-0.56) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 9.3%        | 95.5%       | 14.1% | 92.9% | 0.52 (0.48-0.56) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 9.5%        | 95.1%       | 13.4% | 93.1% | 0.52 (0.48-0.57) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 7.7%        | 96.5%       | 14.7% | 93.0% | 0.52 (0.48-0.56) |
| HC <10 <sup>th</sup> MGRS                | 11.0%       | 95.5%       | 16.2% | 93.1% | 0.53 (0.49-0.57) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 4.4%        | 97.5%       | 12.5% | 92.7% | 0.51 (0.47-0.55) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 8.3%        | 90.8%       | 6.6%  | 92.6% | 0.50 (0.46-0.54) |
| PI-for-age <10 <sup>th</sup> percentile  | 7.3%        | 90.0%       | 5.5%  | 92.5% | 0.48 (0.45-0.53) |
| BMI <10 <sup>th</sup> percentile         | 11.9%       | 90.7%       | 9.2%  | 92.9% | 0.51 (0.47-0.55) |
| BMI-for-age <10 <sup>th</sup> percentile | 12.4%       | 90.9%       | 9.6%  | 92.9% | 0.52 (0.48-0.56) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 9.1%        | 90.9%       | 7.2%  | 92.7% | 0.50 (0.46-0.54) |
| HC/PI >90 <sup>th</sup> percentile       | 3.7%        | 92.2%       | 3.6%  | 92.4% | 0.48 (0.44-0.52) |
| HC/BMI >90 <sup>th</sup> percentile      | 8.7%        | 92.0%       | 7.9%  | 92.7% | 0.50 (0.46-0.54) |

**Table S7.8. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in INTERGROWTH-21<sup>st</sup> in males**

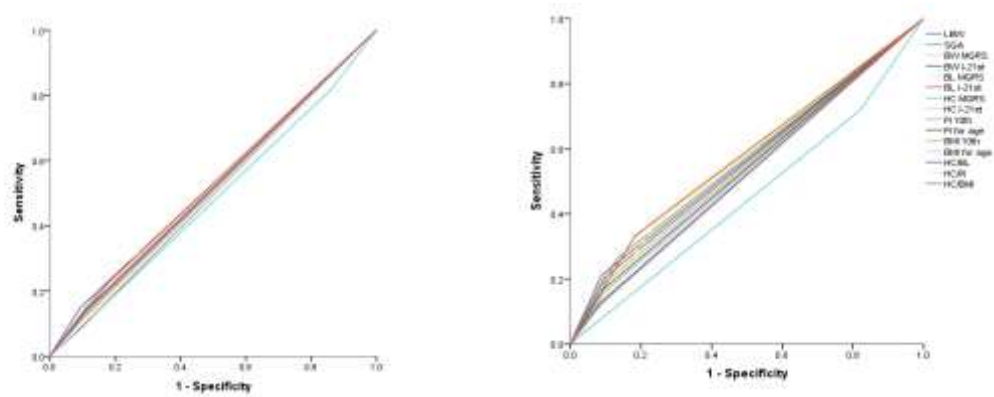
| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 2.8%        | 95.8%       | 4.5%  | 93.2% | 0.48 (0.39-0.58) |
| SGA                                      | 17.1%       | 81.8%       | 6.2%  | 93.3% | 0.49 (0.40-0.59) |
| BW <10 <sup>th</sup> MGRS                | 22.2%       | 84.3%       | 9.3%  | 93.7% | 0.52 (0.42-0.62) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 13.9%       | 89.5%       | 8.8%  | 93.5% | 0.52 (0.42-0.62) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 16.7%       | 87.9%       | 9.1%  | 93.6% | 0.51 (0.41-0.61) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 14.3%       | 92.1%       | 11.4% | 93.8% | 0.53 (0.43-0.64) |
| HC <10 <sup>th</sup> MGRS                | 16.7%       | 87.3%       | 8.7%  | 93.5% | 0.51 (0.41-0.61) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 11.4%       | 93.7%       | 11.4% | 97.3% | 0.53 (0.42-0.63) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 11.1%       | 89.9%       | 7.4%  | 93.3% | 0.49 (0.39-0.59) |
| PI-for-age <10 <sup>th</sup> percentile  | 11.4%       | 90.1%       | 7.5%  | 93.5% | 0.51 (0.41-0.61) |
| BMI <10 <sup>th</sup> percentile         | 8.3%        | 89.7%       | 5.6%  | 93.1% | 0.48 (0.38-0.58) |
| BMI-for-age <10 <sup>th</sup> percentile | 8.6%        | 89.3%       | 5.4%  | 93.2% | 0.49 (0.39-0.59) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 11.1%       | 90.1%       | 7.5%  | 93.3% | 0.49 (0.40-0.59) |
| HC/PI >90 <sup>th</sup> percentile       | 13.9%       | 88.7%       | 8.2%  | 93.4% | 0.50 (0.40-0.60) |
| HC/BMI >90 <sup>th</sup> percentile      | 11.1%       | 90.3%       | 7.7%  | 93.3% | 0.49 (0.40-0.59) |



**Table S7.9. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and attention impairment in INTERGROWTH-21<sup>st</sup> in females**

| Variables                                | Sensitivity | Specificity | PPV  | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |      |       |                  |
| BW <2500g                                | 0.0%        | 91.3%       | 0.0% | 95.2% | 0.46 (0.35-0.57) |
| SGA                                      | 25.0%       | 75.2%       | 4.5% | 95.6% | 0.50 (0.38-0.62) |
| BW <10 <sup>th</sup> MGRS                | 20.8%       | 80.5%       | 4.7% | 95.7% | 0.51 (0.39-0.63) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 12.5%       | 86.7%       | 4.2% | 95.5% | 0.50 (0.38-0.61) |
| <b>Stunting indices</b>                  |             |             |      |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 12.5%       | 84.9%       | 3.7% | 95.4% | 0.49 (0.37-0.61) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 20.8%       | 88.9%       | 8.1% | 96.0% | 0.55 (0.42-0.67) |
| HC <10 <sup>th</sup> MGRS                | 12.5%       | 84.7%       | 3.7% | 95.4% | 0.49 (0.37-0.61) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 12.5%       | 92.6%       | 7.3% | 95.8% | 0.53 (0.40-0.65) |
| <b>Wasting indices</b>                   |             |             |      |       |                  |
| PI <10 <sup>th</sup> percentile          | 8.3%        | 89.9%       | 3.7% | 95.5% | 0.49 (0.38-0.61) |
| PI-for-age <10 <sup>th</sup> percentile  | 12.5%       | 90.4%       | 5.8% | 95.7% | 0.52 (0.39-0.64) |
| BMI <10 <sup>th</sup> percentile         | 4.2%        | 89.7%       | 1.9% | 95.3% | 0.47(0.36-0.58)  |
| BMI-for-age <10 <sup>th</sup> percentile | 12.5%       | 89.9%       | 5.5% | 95.6% | 0.51 (0.39-0.63) |
| <b>Asymmetry indices</b>                 |             |             |      |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 12.5%       | 90.9%       | 6.0% | 95.7% | 0.52 (0.40-0.64) |
| HC/PI >90 <sup>th</sup> percentile       | 8.3%        | 91.1%       | 4.2% | 95.5% | 0.50 (0.38-0.61) |
| HC/BMI >90 <sup>th</sup> percentile      | 8.4%        | 89.3%       | 3.5% | 95.4% | 0.49 (0.37-0.61) |

## Pelotas



**ALSPAC**

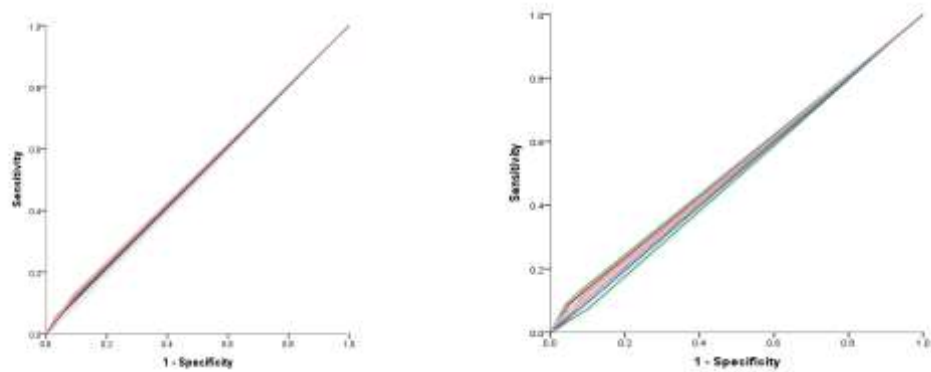
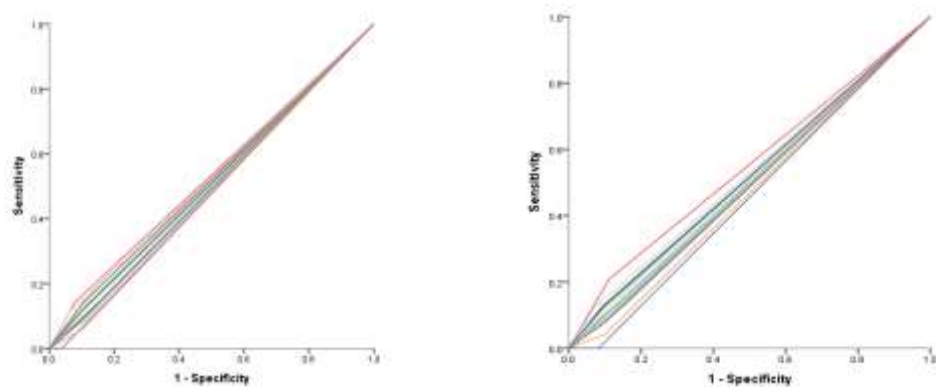
**INTERGROWTH-21st**

**Figure S7.1. Receiver operator characteristic (ROC) curves for attention outcomes in males (left) and females (right)**

**Table S7.10. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in Pelotas in males**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)       |
|------------------------------------------|-------------|-------------|-------|-------|--------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                    |
| BW <2500g                                | 12.5%       | 93.2%       | 31.8% | 80.9% | 0.53 (0.50-0.56)   |
| SGA                                      | 21.1%       | 86.1%       | 27.5% | 81.3% | 0.53 (0.50-0.57)   |
| BW <10 <sup>th</sup> MGRS                | 26.3%       | 84.0%       | 29.3% | 81.9% | 0.55 (0.52-0.58)*  |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 13.9%       | 91.4%       | 28.7% | 80.9% | 0.52 (0.49-0.56)   |
| <b>Stunting indices</b>                  |             |             |       |       |                    |
| BL < 10 <sup>th</sup> MGRS               | 39.1%       | 74.3%       | 27.5% | 83.0% | 0.57 (0.53-0.60)** |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 24.7%       | 83.5%       | 27.1% | 81.7% | 0.54 (0.51-0.57)   |
| HC <10 <sup>th</sup> MGRS                | 23.5%       | 88.3%       | 33.5% | 82.2% | 0.56 (0.53-0.59)** |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 11.2%       | 94.3%       | 32.8% | 81.0% | 0.53 (0.49-0.56)   |
| <b>Wasting indices</b>                   |             |             |       |       |                    |
| PI <10 <sup>th</sup> percentile          | 12.7%       | 90.6%       | 25.3% | 80.6% | 0.52 (0.48-0.55)   |
| PI-for-age <10 <sup>th</sup> percentile  | 10.2%       | 90.4%       | 20.7% | 80.2% | 0.50 (0.47-0.54)   |
| BMI <10 <sup>th</sup> percentile         | 14.8%       | 91.2%       | 29.5% | 81.1% | 0.53 (0.50-0.56)   |
| BMI-for-age <10 <sup>th</sup> percentile | 11.5%       | 90.6%       | 23.3% | 80.5% | 0.51 (0.48-0.54)   |
| <b>Asymmetry indices</b>                 |             |             |       |       |                    |
| HC/BL >90 <sup>th</sup> percentile       | 15.5%       | 90.0%       | 27.9% | 81.0% | 0.53 (0.49-0.56)   |
| HC/PI >90 <sup>th</sup> percentile       | 11.4%       | 87.0%       | 18.0% | 79.8% | 0.49 (0.46-0.52)   |
| HC/BMI >90 <sup>th</sup> percentile      | 15.5%       | 90.1%       | 28.0% | 81.0% | 0.53 (0.49-0.56)   |

**Table S7.11. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in Pelotas in females**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)       |
|------------------------------------------|-------------|-------------|-------|-------|--------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                    |
| BW <2500g                                | 20.8%       | 91.2%       | 25.8% | 88.7% | 0.56 (0.52-0.60)*  |
| SGA                                      | 21.2%       | 86.9%       | 19.2% | 88.3% | 0.54 (0.50-0.58)*  |
| BW <10 <sup>th</sup> MGRS                | 31.6%       | 82.8%       | 21.3% | 89.2% | 0.57 (0.53-0.62)** |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 16.0%       | 91.4%       | 21.5% | 88.1% | 0.54 (0.50-0.58)   |
| <b>Stunting indices</b>                  |             |             |       |       |                    |
| BL < 10 <sup>th</sup> MGRS               | 36.8%       | 73.0%       | 16.7% | 88.7% | 0.55 (0.51-0.59)*  |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 28.7%       | 81.9%       | 18.9% | 88.7% | 0.55 (0.51-0.60)*  |
| HC <10 <sup>th</sup> MGRS                | 65.4%       | 16.2%       | 10.3% | 76.0% | 0.59 (0.55-0.63)** |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 15.7%       | 93.0%       | 24.8% | 88.3% | 0.54 (0.50-0.59)*  |
| <b>Wasting indices</b>                   |             |             |       |       |                    |
| PI <10 <sup>th</sup> percentile          | 15.7%       | 90.8%       | 20.0% | 88.0% | 0.53 (0.49-0.57)   |
| PI-for-age <10 <sup>th</sup> percentile  | 12.6%       | 90.7%       | 16.6% | 87.6% | 0.52 (0.48-0.56)   |
| BMI <10 <sup>th</sup> percentile         | 20.4%       | 91.6%       | 26.3% | 88.7% | 0.56 (0.52-0.60)*  |
| BMI-for-age <10 <sup>th</sup> percentile | 13.9%       | 90.9%       | 18.3% | 87.8% | 0.52 (0.48-0.57)   |
| <b>Asymmetry indices</b>                 |             |             |       |       |                    |
| HC/BL >90 <sup>th</sup> percentile       | 8.7%        | 91.4%       | 12.9% | 87.1% | 0.50 (0.46-0.54)   |
| HC/PI >90 <sup>th</sup> percentile       | 7.4%        | 92.9%       | 13.3% | 87.2% | 0.50 (0.46-0.54)   |
| HC/BMI >90 <sup>th</sup> percentile      | 13.5%       | 91.8%       | 19.5% | 87.9% | 0.53 (0.49-0.57)   |

**Table S7.12. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in ALSPAC in males**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 5.3%        | 97.1%       | 27.8% | 83.0% | 0.51 90.44-0.57) |
| SGA                                      | 9.6%        | 92.4%       | 20.9% | 83.0% | 0.51 (0.44-0.57) |
| BW <10 <sup>th</sup> MGRS                | 9.6%        | 91.5%       | 19.1% | 82.9% | 0.50 (0.43-0.56) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 75%         | 95.3%       | 25.0% | 83.3% | 0.52 (0.45-0.58) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 6.4%        | 94.0%       | 18.2% | 82.7% | 0.50 (0.43-0.56) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 4.3%        | 97.3%       | 25.0% | 82.9% | 0.50 90.44-0.57) |
| HC <10 <sup>th</sup> MGRS                | 5.3%        | 96.0%       | 21.7% | 82.9% | 0.50 (0.44-0.57) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 3.2%        | 98.7%       | 33.3% | 83.0% | 0.51 (0.44-0.58) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 13.0%       | 87.2%       | 17.4% | 82.9% | 0.50 (0.44-0.57) |
| PI-for-age <10 <sup>th</sup> percentile  | 9.8%        | 87.4%       | 13.8% | 82.4% | 0.49 (0.42-0.55) |
| BMI <10 <sup>th</sup> percentile         | 10.9%       | 89.4%       | 17.5% | 82.9% | 0.50 (0.44-0.57) |
| BMI-for-age <10 <sup>th</sup> percentile | 10.9%       | 89.9%       | 18.2% | 83.0% | 0.51 (0.44-0.57) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 6.4%        | 94.0%       | 18.2% | 82.7% | 0.50 (0.44-0.57) |
| HC/PI >90 <sup>th</sup> percentile       | 9.8%        | 86.5%       | 13.0% | 82.3% | 0.48 (0.42-0.55) |
| HC/BMI >90 <sup>th</sup> percentile      | 12.0%       | 88.1%       | 17.2% | 82.9% | 0.50 (0.44-0.57) |

**Table S7.13. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in ALSPAC in females**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 0.0%        | 96.9%       | 0.0%  | 96.9% | 0.49 (0.41-0.56) |
| SGA                                      | 5.2%        | 94.5%       | 12.5% | 86.8% | 0.50 (0.42-0.58) |
| BW <10 <sup>th</sup> MGRS                | 3.4%        | 94.3%       | 8.3%  | 86.6% | 0.49 (0.41-0.57) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 5.2%        | 96.4%       | 17.6% | 87.1% | 0.51 (0.43-0.59) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 1.8%        | 96.6%       | 7.1%  | 86.7% | 0.49 (0.41-0.57) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 3.5%        | 97.6%       | 18.2% | 87.1% | 0.51 (0.43-0.59) |
| HC <10 <sup>th</sup> MGRS                | 3.5%        | 96.1%       | 11.8% | 87.0% | 0.50 (0.42-0.58) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 5.3%        | 97.6%       | 25.0% | 87.4% | 0.52 (0.44-0.60) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 14.0%       | 90.2%       | 17.8% | 87.4% | 0.52 (0.44-0.60) |
| PI-for-age <10 <sup>th</sup> percentile  | 15.8%       | 90.2%       | 19.6% | 87.6% | 0.53 (0.45-0.61) |
| BMI <10 <sup>th</sup> percentile         | 8.8%        | 89.7%       | 11.4% | 86.7% | 0.49 (0.41-0.57) |
| BMI-for-age <10 <sup>th</sup> percentile | 14.0%       | 90.5%       | 18/2% | 87.4% | 0.52 (0.44-0.61) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 5.3%        | 93.1%       | 10.3% | 86.7% | 0.49 (0.41-0.57) |
| HC/PI >90 <sup>th</sup> percentile       | 12.3%       | 92.0%       | 18.9% | 87.4% | 0.52 (0.44-0.60) |
| HC/BMI >90 <sup>th</sup> percentile      | 10.5%       | 91.2%       | 15.4% | 87.1% | 0.51 (0.43-0.59) |

**Table S7.14. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in INTERGROWTH-21<sup>st</sup> in males**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 5.3%        | 95.9%       | 30.4% | 75.1% | 0.50 (0.44-0.56) |
| SGA                                      | 17.7%       | 83.0%       | 25.6% | 75.3% | 0.50 (0.45-0.56) |
| BW <10 <sup>th</sup> MGRS                | 17.4%       | 85.0%       | 28.0% | 75.5% | 0.51 (0.45-0.56) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 14.4%       | 90.6%       | 33.9% | 76.0% | 0.53 (0.47-0.58) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 10.6%       | 86.3%       | 20.6% | 74.2% | 0.48 (0.43-0.54) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 6.2%        | 90.3%       | 17.4% | 74.4% | 0.48 (0.43-0.54) |
| HC <10 <sup>th</sup> MGRS                | 15.9%       | 88.3%       | 31.3% | 75.7% | 0.52 (0.46-0.57) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 7.7%        | 94.4%       | 31.2% | 75.5% | 0.51 (0.45-0.57) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 15.2%       | 92.4%       | 40.0% | 76.4% | 0.54 (0.47-0.58) |
| PI-for-age <10 <sup>th</sup> percentile  | 15.4%       | 91.8%       | 38.5% | 76.6% | 0.54 (0.48-0.60) |
| BMI <10 <sup>th</sup> percentile         | 13.6%       | 91.9%       | 36.0% | 76.0% | 0.52 (0.46-0.58) |
| BMI-for-age <10 <sup>th</sup> percentile | 13.1%       | 90.6%       | 31.5% | 75.9% | 0.52 90.46-0.58) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 11.4%       | 89.0%       | 25.9% | 89.0% | 0.50 (0.44-0.56) |
| HC/PI >90 <sup>th</sup> percentile       | 15.9%       | 90.6%       | 36.2% | 76.2% | 0.53 (0.44-0.55) |
| HC/BMI >90 <sup>th</sup> percentile      | 14.4%       | 92.6%       | 39.6% | 76.3% | 0.53 (0.47-0.59) |

**Table S7.15. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) for birth anthropometric indices and cognitive impairment in INTERGROWTH-21<sup>st</sup> in females**

| Variables                                | Sensitivity | Specificity | PPV   | NPV   | AUC (95% CI)     |
|------------------------------------------|-------------|-------------|-------|-------|------------------|
| <b>Birth weight indices</b>              |             |             |       |       |                  |
| BW <2500g                                | 8.2%        | 91.4%       | 17.4% | 81.8% | 0.50 (0.44-0.57) |
| SGA                                      | 24.5%       | 75.5%       | 18.2% | 81.8% | 0.50 (0.44-0.56) |
| BW <10 <sup>th</sup> MGRS                | 24.1%       | 80.8%       | 19.8% | 82.3% | 0.49 (0.45-0.58) |
| BW <10 <sup>th</sup> I-21 <sup>st</sup>  | 12.2%       | 86.4%       | 16.7% | 81.6% | 0.49 (0.43-0.56) |
| <b>Stunting indices</b>                  |             |             |       |       |                  |
| BL < 10 <sup>th</sup> MGRS               | 11.3%       | 83.8%       | 13.4% | 81.0% | 0.48 (0.41-0.54) |
| BL <10 <sup>th</sup> I-21 <sup>st</sup>  | 12.4%       | 88.3%       | 19.0% | 82.0% | 0.50 (0.44-0.57) |
| HC <10 <sup>th</sup> MGRS                | 20.6%       | 85.6%       | 24.1% | 83.0% | 0.53 (0.47-0.60) |
| HC <10 <sup>th</sup> I-21 <sup>st</sup>  | 9.3%        | 92.9%       | 22.5% | 92.2% | 0.51 (0.45-0.58) |
| <b>Wasting indices</b>                   |             |             |       |       |                  |
| PI <10 <sup>th</sup> percentile          | 12.4%       | 91.3%       | 24.0% | 82.5% | 0.52 (0.45-0.58) |
| PI-for-age <10 <sup>th</sup> percentile  | 10.3%       | 91.3%       | 20.8% | 82.1% | 0.51 (0.44-0.57) |
| BMI <10 <sup>th</sup> percentile         | 14.4%       | 91.1%       | 26.4% | 82.8% | 0.53 (0.46-0.59) |
| BMI-for-age <10 <sup>th</sup> percentile | 11.3%       | 90.6%       | 21.2% | 82.2% | 0.51 (0.45-0.57) |
| <b>Asymmetry indices</b>                 |             |             |       |       |                  |
| HC/BL >90 <sup>th</sup> percentile       | 4.1%        | 89.0%       | 7.7%  | 80.7% | 0.47 (0.41-0.53) |
| HC/PI >90 <sup>th</sup> percentile       | 9.3%        | 92.4%       | 21.4% | 82.1% | 0.51 (0.41-0.57) |
| HC/BMI >90 <sup>th</sup> percentile      | 10.3%       | 90.2%       | 18.9% | 81.9% | 0.50 (0.44-0.57) |



## Pelotas

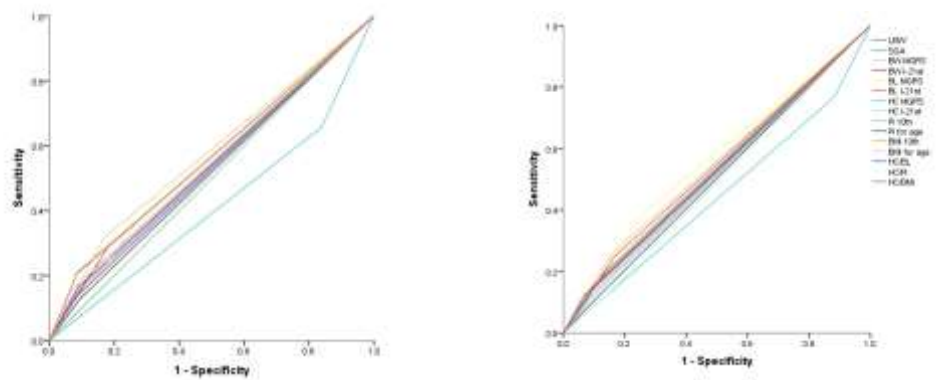
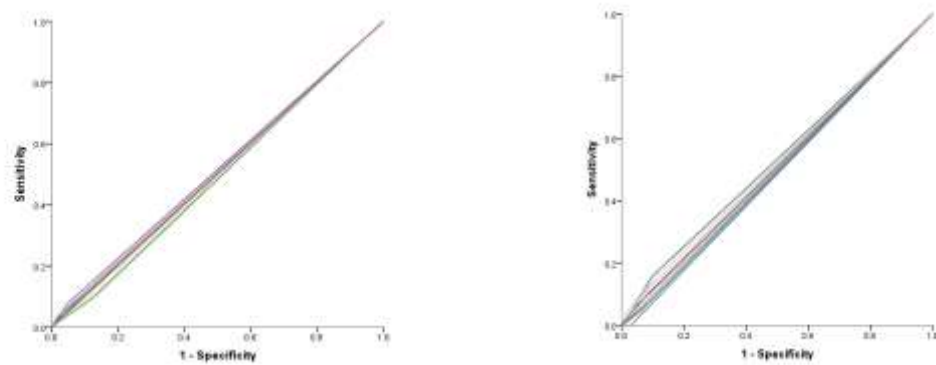
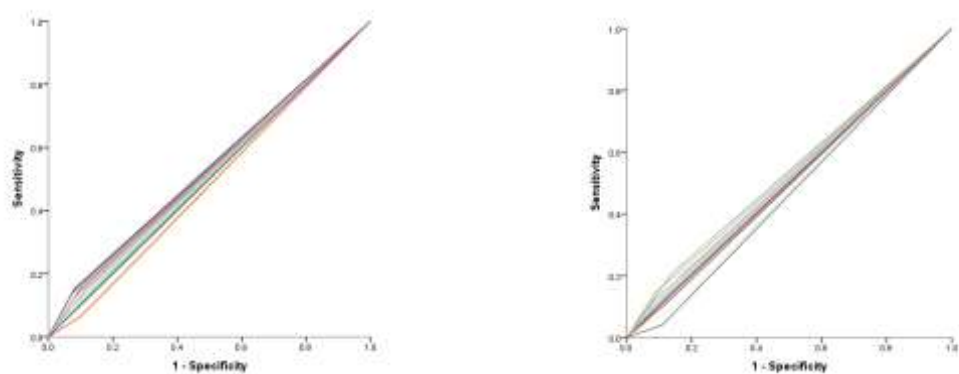
**ALSPAC****INTERGROWTH-21<sup>st</sup>**

**Figure S7.2. Receiver operator characteristic (ROC) curves for cognitive outcomes in males (left) and females (right)**

## Appendix II: PRISMA Statement

| TITLE                              |                                                                                                                                                                                                                                                                                                             |     |
|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Title                              | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                                                                                                         | yes |
| ABSTRACT                           |                                                                                                                                                                                                                                                                                                             |     |
| Structured summary                 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | yes |
| INTRODUCTION                       |                                                                                                                                                                                                                                                                                                             |     |
| Rationale                          | Describe the rationale for the review in the context of what is already known.                                                                                                                                                                                                                              | yes |
| Objectives                         | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                                                                  | yes |
| METHODS                            |                                                                                                                                                                                                                                                                                                             |     |
| Protocol and registration          | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                                                                                                               | yes |
| Eligibility criteria               | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                                                                                      | yes |
| Information sources                | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                                                  | yes |
| Search                             | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                                               | yes |
| Study selection                    | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                                   | yes |
| Data collection process            | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                                  | yes |
| Data items                         | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                                                                                                       | yes |
| Risk of bias in individual studies | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                                                                                      | yes |
| Summary measures                   | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                                                                                                               | yes |
| Synthesis of results               | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.                                                                                                                                                   | yes |
| Risk of bias across studies        | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                                                                                                                                | yes |
| Additional analyses                | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                                                                                                            | yes |
| RESULTS                            |                                                                                                                                                                                                                                                                                                             |     |
| Study selection                    | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                                                                                                             | yes |
| Study characteristics              | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                                                                                                                | yes |
| Risk of bias within studies        | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                                                                                                                   | yes |

|                               |                                                                                                                                                                                                          |            |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Results of individual studies | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | <b>yes</b> |
| Synthesis of results          | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                  | <b>yes</b> |
| Risk of bias across studies   | Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                          | <b>yes</b> |
| Additional analysis           | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                    | <b>yes</b> |
| <b>DISCUSSION</b>             |                                                                                                                                                                                                          |            |
| Summary of evidence           | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                     | <b>yes</b> |
| Limitations                   | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                            | <b>yes</b> |
| Conclusions                   | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                  | <b>yes</b> |
| <b>FUNDING</b>                |                                                                                                                                                                                                          |            |
| Funding                       | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                               | <b>n/a</b> |

# Appendix III: Child Behaviour Checklist Record Form (Example)

Please print. Be sure to answer all items.

Below is a list of items that describe children and youths. For each item that describes your child **now or within the past 6 months**, please circle the **2** if the item is **very true or often true** of your child. Circle the **1** if the item is **somewhat or sometimes true** of your child. If the item is **not true** of your child, circle the **0**. Please answer all items as well as you can, even if some do not seem to apply to your child.

| 0 = Not True (as far as you know) | 1 = Somewhat or Sometimes True | 2 = Very True or Often True                                                                                   |
|-----------------------------------|--------------------------------|---------------------------------------------------------------------------------------------------------------|
| 0 1 <b>2</b>                      |                                | 1. Acts too young for his/her age                                                                             |
| 0 <b>1</b> 2                      |                                | <sup>a</sup> 2. Drinks alcohol without parents' approval (describe): <b>3x</b>                                |
| 0 1 <b>2</b>                      |                                | 3. Argues a lot                                                                                               |
| 0 1 <b>2</b>                      |                                | <sup>a</sup> 4. Fails to finish things he/she starts                                                          |
| 0 1 <b>2</b>                      |                                | <sup>a</sup> 5. There is very little he/she enjoys                                                            |
| <b>0</b> 1 2                      |                                | 6. Bowel movements outside toilet                                                                             |
| <b>0</b> 1 2                      |                                | 7. Bragging, boasting                                                                                         |
| 0 1 <b>2</b>                      |                                | 8. Can't concentrate, can't pay attention for long                                                            |
| 0 1 <b>2</b>                      |                                | 9. Can't get his/her mind off certain thoughts; obsessions (describe): <b>computers; people who cross him</b> |
| <b>0</b> 1 2                      |                                | 10. Can't sit still, restless, or hyperactive                                                                 |
| <b>0</b> 1 2                      |                                | 11. Clings to adults or too dependent                                                                         |
| 0 1 <b>2</b>                      |                                | 12. Complains of loneliness                                                                                   |
| 0 1 <b>2</b>                      |                                | 13. Confused or seems to be in a fog                                                                          |
| <b>0</b> 1 2                      |                                | 14. Cries a lot                                                                                               |
| <b>0</b> 1 2                      |                                | 15. Cruel to animals                                                                                          |
| 0 1 <b>2</b>                      |                                | 16. Cruelty, bullying, or meanness to others                                                                  |
| 0 1 <b>2</b>                      |                                | 17. Daydreams or gets lost in his/her thoughts                                                                |
| <b>0</b> 1 2                      |                                | 18. Deliberately harms self or attempts suicide                                                               |
| <b>0</b> 1 2                      |                                | 19. Demands a lot of attention                                                                                |
| <b>0</b> 1 2                      |                                | 20. Destroys his/her own things                                                                               |
| <b>0</b> 1 2                      |                                | 21. Destroys things belonging to his/her family or others                                                     |
| 0 1 <b>2</b>                      |                                | 22. Disobedient at home                                                                                       |
| <b>0</b> 1 2                      |                                | 23. Disobedient at school                                                                                     |
| 0 <b>1</b> 2                      |                                | 24. Doesn't eat well                                                                                          |
| 0 1 <b>2</b>                      |                                | 25. Doesn't get along with other kids                                                                         |
| 0 <b>1</b> 2                      |                                | 26. Doesn't seem to feel guilty after misbehaving                                                             |
| 0 1 <b>2</b>                      |                                | 27. Easily jealous                                                                                            |
| 0 <b>1</b> 2                      |                                | <sup>a</sup> 28. Breaks rules at home, school, or elsewhere                                                   |
| <b>0</b> 1 2                      |                                | 29. Fears certain animals, situations, or places, other than school (describe):                               |
| 0 <b>1</b> 2                      |                                | 30. Fears going to school                                                                                     |
| <b>0</b> 1 2                      |                                | 31. Fears he/she might think or do something bad                                                              |
| <b>0</b> 1 2                      |                                | 32. Feels he/she has to be perfect                                                                            |
| 0 1 <b>2</b>                      |                                | 33. Feels or complains that no one loves him/her                                                              |
| 0 1 <b>2</b>                      |                                | 34. Feels others are out to get him/her                                                                       |
| 0 1 <b>2</b>                      |                                | 35. Feels worthless or inferior                                                                               |
| <b>0</b> 1 2                      |                                | 36. Gets hurt a lot, accident-prone                                                                           |
| 0 <b>1</b> 2                      |                                | 37. Gets in many fights                                                                                       |
| <b>0</b> 1 2                      |                                | 38. Gets teased a lot                                                                                         |
| <b>0</b> 1 2                      |                                | 39. Hangs around with others who get in trouble                                                               |
| <b>0</b> 1 2                      |                                | 40. Hears sound or voices that aren't there (describe):                                                       |
| 0 <b>1</b> 2                      |                                | 41. Impulsive or acts without thinking                                                                        |
| 0 <b>1</b> 2                      |                                | 42. Would rather be alone than with others                                                                    |
| <b>0</b> 1 2                      |                                | 43. Lying or cheating                                                                                         |
| <b>0</b> 1 2                      |                                | 44. Bites fingernails                                                                                         |
| 0 1 <b>2</b>                      |                                | 45. Nervous, highstrung, or tense                                                                             |
| <b>0</b> 1 2                      |                                | 46. Nervous movements or twitching (describe):                                                                |
| <b>0</b> 1 2                      |                                | 47. Nightmares                                                                                                |
| <b>0</b> 1 2                      |                                | 48. Not liked by other kids                                                                                   |
| <b>0</b> 1 2                      |                                | 49. Constipated, doesn't move bowels                                                                          |
| <b>0</b> 1 2                      |                                | 50. Too fearful or anxious                                                                                    |
| <b>0</b> 1 2                      |                                | 51. Feels dizzy or lightheaded                                                                                |
| <b>0</b> 1 2                      |                                | 52. Feels too guilty                                                                                          |
| <b>0</b> 1 2                      |                                | 53. Overeating                                                                                                |
| <b>0</b> 1 2                      |                                | 54. Overtired without good reason                                                                             |
| <b>0</b> 1 2                      |                                | 55. Overweight                                                                                                |
|                                   |                                | 56. Physical problems <b>without known medical cause:</b>                                                     |
| <b>0</b> 1 2                      |                                | a. Aches or pains ( <b>not</b> stomach or headaches)                                                          |
| 0 1 <b>2</b>                      |                                | b. Headaches                                                                                                  |
| <b>0</b> 1 2                      |                                | c. Nausea, feels sick                                                                                         |
| <b>0</b> 1 2                      |                                | d. Problems with eyes ( <b>not</b> if corrected by glasses) (describe):                                       |
| <b>0</b> 1 2                      |                                | e. Rashes or other skin problems                                                                              |
| <b>0</b> 1 2                      |                                | f. Stomachaches                                                                                               |
| <b>0</b> 1 2                      |                                | g. Vomiting, throwing up                                                                                      |
| <b>0</b> 1 2                      |                                | h. Other (describe):                                                                                          |

PAGE 3 Be sure you answered all items. Then see other side.

**Please print. Be sure to answer all items.**

| 0 = Not True (as far as you know)                                                                                                                | 1 = Somewhat or Sometimes True                                                                                                                                               | 2 = Very True or Often True |
|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 57. Physically attacks people                                            | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 84. Strange behavior (describe): _____                                                               |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 58. Picks nose, skin, or other parts of body (describe): _____           | <input type="radio"/> 0 <input checked="" type="radio"/> 1 <input type="radio"/> 2 85. Strange ideas (describe): <u>Peculiar beliefs about his teachers</u>                  |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 59. Plays with own sex parts in public                                   | <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 86. Stubborn, sullen, or irritable                                                        |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 60. Plays with own sex parts too much                                    | <input type="radio"/> 0 <input checked="" type="radio"/> 1 <input type="radio"/> 2 87. Sudden changes in mood or feelings                                                    |                             |
| <input type="radio"/> 0 <input checked="" type="radio"/> 1 <input type="radio"/> 2 61. Poor school work                                          | <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 88. Sulks a lot                                                                           |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 62. Poorly coordinated or clumsy                                         | <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 89. Suspicious                                                                            |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 63. Prefers being with older kids                                        | <input type="radio"/> 0 <input checked="" type="radio"/> 1 <input type="radio"/> 2 90. Swearing or obscene language                                                          |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 64. Prefers being with younger kids                                      | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 91. Talks about killing self                                                                         |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 65. Refuses to talk                                           | <input type="radio"/> 0 <input checked="" type="radio"/> 1 <input type="radio"/> 2 92. Talks or walks in sleep (describe): _____                                             |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 66. Repeats certain acts over and over; compulsions (describe): _____    | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 93. Talks too much                                                                                   |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 67. Runs away from home                                                  | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 94. Teases a lot                                                                                     |                             |
| <input type="radio"/> 0 <input checked="" type="radio"/> 1 <input type="radio"/> 2 68. Screams a lot                                             | <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 95. Temper tantrums or hot temper                                                         |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 69. Secretive, keeps things to self                           | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 96. Thinks about sex too much                                                                        |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 70. Sees things that aren't there (describe): _____                      | <input type="radio"/> 0 <input checked="" type="radio"/> 1 <input type="radio"/> 2 97. Threatens people                                                                      |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 71. Self-conscious or easily embarrassed                      | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 98. Thumb-sucking                                                                                    |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 72. Sets fires                                                           | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 99. Smokes, chews, or sniffs tobacco                                                                 |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 73. Sexual problems (describe): _____                                    | <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 100. Trouble sleeping (describe): _____                                                   |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 74. Showing off or clowning                                              | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 101. Truancy, skips school                                                                           |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 75. Too shy or timid                                                     | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 102. Underactive, slow moving, or lacks energy                                                       |                             |
| <input type="radio"/> 0 <input checked="" type="radio"/> 1 <input type="radio"/> 2 76. Sleeps less than most kids                                | <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 103. Unhappy, sad, or depressed                                                           |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 77. Sleeps more than most kids during day and/or night (describe): _____ | <input type="radio"/> 0 <input checked="" type="radio"/> 1 <input type="radio"/> 2 104. Unusually loud                                                                       |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 78. Inattentive or easily distracted                          | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 105. Uses drugs for nonmedical purposes ( <u>don't</u> include alcohol or tobacco) (describe): _____ |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 79. Speech problem (describe): _____                                     | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 106. Vandalism                                                                                       |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 80. Stares blankly                                            | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 107. Wets self during the day                                                                        |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 81. Steals at home                                                       | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 108. Wets the bed                                                                                    |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 82. Steals outside the home                                              | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 109. Whining                                                                                         |                             |
| <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 83. Stores up too many things he/she doesn't need (describe): _____      | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 110. Wishes to be of opposite sex                                                                    |                             |
|                                                                                                                                                  | <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 111. Withdrawn, doesn't get involved with others                                          |                             |
|                                                                                                                                                  | <input type="radio"/> 0 <input type="radio"/> 1 <input checked="" type="radio"/> 2 112. Worries                                                                              |                             |
|                                                                                                                                                  | 113. Please write in any problems your child has that were not listed above: _____                                                                                           |                             |
|                                                                                                                                                  | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 _____                                                                                                |                             |
|                                                                                                                                                  | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 _____                                                                                                |                             |
|                                                                                                                                                  | <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 _____                                                                                                |                             |

PAGE 4 **Please be sure you answered all items.**

## Appendix IV: Pelotas Perinatal Interview Form Extract (English Translation)

|                                                                                   |                 |                                                                                     |
|-----------------------------------------------------------------------------------|-----------------|-------------------------------------------------------------------------------------|
|  | <p>! # # \$</p> |  |
|-----------------------------------------------------------------------------------|-----------------|-------------------------------------------------------------------------------------|

| BLOCK A - IDENTIFICATION                                                         |       |                                                                                            |
|----------------------------------------------------------------------------------|-------|--------------------------------------------------------------------------------------------|
| Identification number RN                                                         |       | LABEL                                                                                      |
| One. Name of interviewer:                                                        | [A01] |                                                                                            |
| 2nd. Hospital RN's birth:                                                        | [A02] | Benef. English first<br>Santa House 2<br>Hosp. Clinics 3<br>Fau 4<br>Piltcher 5<br>Other 6 |
| Another: _____                                                                   |       |                                                                                            |
| 3rd. Name complete the mother of the newborn (case no accent):                   |       |                                                                                            |
| 4th. Date of Birth RN (DD / MM):                                                 | [A03] | ____ / ____                                                                                |
| 5th. Time of Birth RN (HH: MM):                                                  | [A04] | ____ : ____                                                                                |
| 6th. Number of children born in childbirth:                                      | [A05] | __ Son (s)                                                                                 |
| If multiple births, twin complete a questionnaire for each child from the second |       |                                                                                            |
| 7th. Sex RN:                                                                     | [A06] | male 1<br>female 2                                                                         |
| Eight. Birthweight:                                                              | [A07] | _____ G                                                                                    |
| 9th. APGAR 1 minute                                                              | [A08] | _____                                                                                      |
| 10. 5th minute APGAR                                                             | [A09] | _____                                                                                      |
| 11. Date and start time of the interview                                         | [A10] | ____ / ____                                                                                |
|                                                                                  | [A11] | ____ : ____                                                                                |

| BLOCK B - DELIVERY OF HEALTH AND NEWBORN                                                                                         |       |                                                                                                              |
|----------------------------------------------------------------------------------------------------------------------------------|-------|--------------------------------------------------------------------------------------------------------------|
| Let's start talking about your delivery                                                                                          |       |                                                                                                              |
| 12. (Warning Do not ask. Registration info). The newborn was alive? [B01]<br>IF YES 16                                           |       | not 0<br>yes 1                                                                                               |
| 13. The baby's death happened before labor or during labor?                                                                      | [B02] | before 1<br>for 2<br>IGN 9                                                                                   |
| 14. Mrs. have any idea what the problem was or what might have caused the death of the baby?<br>IF NO 16                         | [B03] | not 0<br>yes 1                                                                                               |
| 15. And what is your idea?<br>_____                                                                                              | [B04] | _____                                                                                                        |
| 16. What name Mrs. want to give the baby? (Case no accent)<br>_____                                                              |       |                                                                                                              |
| 17. What Ms. felt that made her come to the hospital?<br><br>Another: _____                                                      | [B05] | bleeding 1<br>lost water 2<br>contraction or pain 3<br>scheduling 4<br>doctor walked 5<br>another 6<br>IGN 9 |
| 18. When the doctor or nurse examined her at the hospital, was okay with your baby?<br>IF YES 21                                 | [B06] | not 0<br>yes 1<br>IGN 9                                                                                      |
| 19. Mrs. know tell us what was wrong?<br>IF NO 21                                                                                | [B07] | not 0<br>yes 1                                                                                               |
| 20. What was it?<br>_____                                                                                                        | [B08] | _____                                                                                                        |
| 21. The doctor or nurse heard the baby's heart beating inside your belly?                                                        | [B09] | not 0<br>yes 1<br>2 was not examined<br>IGN 9                                                                |
| 22. When Mrs. was hospitalized was feeling labor pains of [B10] childbirth?                                                      |       | not 0<br>yes 1<br>IGN 9                                                                                      |
| 23. It was necessary to break the bag, put serum or remedy underneath to start labor or to help the baby to be born?<br>IF NO 25 | [B11] | not 0<br>yes 1<br>IGN 9                                                                                      |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |       |                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24. Because it was necessary to help the baby to be born?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | [B12] | spent time 1<br>High pressure 2<br>broke the bag 3<br>blood does not mix 4<br>the baby was dead 5<br>doctor wanted 6<br>stopped labor 7<br>another reason 8<br>IGN 9                                                                                                                                                                       |
| Another reason: _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |       |                                                                                                                                                                                                                                                                                                                                            |
| 25. Once admitted, who accompanied Mrs. hospital during the labor to get the baby?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | [B13] | doctor 1<br>Student 2<br>nurse or midwife 3<br>nobody followed 4<br>IGN 9                                                                                                                                                                                                                                                                  |
| 26. Who did your labor?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | [B14] | doctor 1<br>Student 2<br>nurse or midwife 3<br>other 4                                                                                                                                                                                                                                                                                     |
| Another person: _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |       |                                                                                                                                                                                                                                                                                                                                            |
| 27. At birth, who attended the baby in the delivery room?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | [B15] | one pediatrician<br>obstetrician 2<br>Student 3<br>nurse or midwife 4<br>5 anesthetist<br>IGN 9                                                                                                                                                                                                                                            |
| 28. The delivery was normal or caesarean?<br>IF CAESAREAN SECTION 32                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | [B16] | 1 Normal<br>Caesarean 2                                                                                                                                                                                                                                                                                                                    |
| 29. Mrs. episiotomy done?<br>(= Cut down episiotomy at delivery)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | [B17] | not 0<br>yes 1<br>IGN 9                                                                                                                                                                                                                                                                                                                    |
| 30. Was used forceps?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | [B18] | not 0<br>yes 1<br>IGN 9                                                                                                                                                                                                                                                                                                                    |
| 31. Analgesia was made?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | [B19] | not 0<br>yes 1<br>IGN 9                                                                                                                                                                                                                                                                                                                    |
| LEAP NOT CONDITIONAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 33    |                                                                                                                                                                                                                                                                                                                                            |
| 32. What was the reason for doing caesarean?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | [B20] | fetal distress 11<br>fetal-pelvic disproportion 12<br>dystocia presentation 13<br>maternal hemorrhage 14<br>stop progression 15<br>eclampsia, pre-eclampsia 16<br>postmaturity 17<br>fetal death 18<br>maternal diabetes 19<br>Repeat 20<br>21 tubal<br>Mom asked 22<br>doctor wanted 23<br>scheduled caesarean 24<br>another 25<br>IGN 99 |
| fetal distress = the heartbeat of the baby fell / the baby pooped inside the womb<br>fetal-pelvic disproportion = small bowl / baby too big<br>dystocia presentation = the baby sitting / in the wrong position<br>maternal hemorrhage = bleeding had<br>= stopped stop progression labor / stop the pain<br>eclampsia, pre-eclampsia, high blood pressure =<br>postmaturity = time spent<br>fetal death = the baby died<br>= maternal diabetes blood sugar<br>= repetition has made another caesarean before<br>= tubal ligation for connecting tubes / deviation to<br>= caesarean mother asked why her mother wanted<br>= doctor wanted to order, the doctor decided he wanted to do caesarean<br>= scheduled caesarean doctor scheduled during pregnancy |       |                                                                                                                                                                                                                                                                                                                                            |
| Another: _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |       |                                                                                                                                                                                                                                                                                                                                            |



|                                                                                                                             |                         |                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------------|----------------------------------------------------------------------|
| Attention! If stillbirth jump to 45                                                                                         |                         |                                                                      |
| 33. <criança> had or is experiencing any health problems?<br>IF NO 36                                                       | [B21]                   | not 0<br>yes 1<br>IGN 9                                              |
| 34. During treatment of <criança>, she needed to stay in the nursery or in ICU?<br><br>IF NO 36                             |                         | not 0<br>yes, one ICU<br>yes, one nursery<br>yes, housing 2<br>IGN 9 |
| 35. What health problem that is presenting or <criança> presented?<br>Problem 1 _____<br>Problem 2 _____<br>Problem 3 _____ | [B23]<br>[B24]<br>[B25] | _____<br>_____<br>_____                                              |
| Now let's talk a little about breastfeeding and nipple                                                                      |                         |                                                                      |
| 36. Mrs.. already put the baby on your chest?<br>IF NO 38                                                                   | [B26]                   | not 0<br>yes 1                                                       |
| 37. How many hours of life Mrs. placed the baby on your chest?<br>(00 = less than 1 hour)                                   | [B27]                   | ____ Hours                                                           |
| 38. Ms. planning to breastfeed her child in the chest?<br>IF NO 40                                                          | [B28]                   | not 0<br>yes 1<br>IGN 9                                              |
| 39. Until what age you want to breastfeed?<br>(77 = as he pleases; 78 = while you milk; 99 = IGN)                           | [B29]                   | by ____ months                                                       |
| 40. Mrs. intends to beak or pacifier to the baby?                                                                           | [B30]                   | not 0<br>yes 1<br>IGN 9                                              |
| 41. Mrs. beak brought to the hospital?                                                                                      | [B31]                   | not 0<br>yes 1<br>IGN 9                                              |
| Since birth, your child has received ...                                                                                    |                         |                                                                      |
| 42. Tea, water or glucose?<br><br>IF YES: How many hours of life?                                                           | [B32]<br><br>[B33]      | not 0<br>yes 1<br>IGN 9<br><br>____ Hours                            |
| 43. Beak or pacifier?<br><br>IF YES: How many hours of life?                                                                | [B34]<br><br>[B35]      | not 0<br>yes 1<br>IGN 9<br><br>____ Hours                            |
| 44. Bottle of milk?<br><br>IF YES: How many hours of life?                                                                  | [B36]<br><br>[B37]      | not 0<br>yes 1<br>IGN 9<br><br>____ Hours                            |

| BLOCK C - PRENATAL AND MORBIDITY GESTATIONAL                                                                                                |       |                                                                                                                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------|
| Now let's talk about your pregnancy                                                                                                         |       |                                                                                                                                 |
| 45. What was the date of your last period?                                                                                                  | [C01] | ___ / ___ / ___                                                                                                                 |
| 46. Mrs. planned to have this child or pregnant unintentionally?                                                                            | [C02] | 1 planned<br>unwittingly 2<br>about 3<br>IGN 9                                                                                  |
| 47. Ms. done any query prenatal during pregnancy?                                                                                           | [C03] | not 0<br>yes 1<br>IGN 9                                                                                                         |
| IF DID NOT PRENATAL 72                                                                                                                      |       |                                                                                                                                 |
| 48. What where Mrs. did his Pre-Natal?                                                                                                      | [C04] | health post 1<br>outpatient HC 2<br>FAU 3<br>medical college (Frigate) 4<br>Charitable clinic 5<br>6 doctor<br>other 7<br>IGN 9 |
| Health Center (name): _____                                                                                                                 |       |                                                                                                                                 |
| Another place - what? _____                                                                                                                 |       |                                                                                                                                 |
| [C05] 49. Mrs. was attended by the same doctor or nurse during prenatal consultations were professionals or different at every appointment? |       | even professional 1<br>two different professional<br>IGN 9                                                                      |
| 50. How many queries prenatal Ms. done?<br>(IGN = 99)                                                                                       | [C06] | ___ Queries                                                                                                                     |
| 51. What month of pregnancy Mrs. made the first prenatal appointment?<br>(IGN = 99)                                                         | [C07] | ___ months                                                                                                                      |
| 52. Mrs. blood tests done during pregnancy? If you did, how many?<br>(00 = not done; 99 = IGN)                                              | [C08] | ___ Exams                                                                                                                       |
| 53. Mrs. urine tests done during pregnancy? If you did, how many?<br>(00 = not done; 99 = IGN)                                              | [C09] | ___ Exams                                                                                                                       |
| 54. What was your weight in early pregnancy?<br>(999 = IGN)                                                                                 | [C10] | ___ Kg                                                                                                                          |
| 55. What was your weight in late pregnancy?<br>(999 = IGN)                                                                                  | [C11] | ___ Kg                                                                                                                          |
| During consultations prenatal doctor or nurse ever ...                                                                                      |       |                                                                                                                                 |
| 56. Asked the date of your last period?                                                                                                     | [C12] | not 0<br>yes 1<br>IGN 9                                                                                                         |
| 57. Verified your weight?                                                                                                                   | [C13] | not 0<br>yes 1<br>IGN 9                                                                                                         |
| 58. Measured your belly?                                                                                                                    | [C14] | not 0<br>yes 1<br>IGN 9                                                                                                         |
| 59. He measured his blood pressure?                                                                                                         | [C15] | not 0<br>yes 1<br>IGN 9                                                                                                         |

|                                                                                                 |       |                                                                              |
|-------------------------------------------------------------------------------------------------|-------|------------------------------------------------------------------------------|
| 60. Did gynecological exam?<br>(If you do not understand, use the term "under examination".)    | [C16] | not 0<br>yes 1<br>IGN 9                                                      |
| 61. Prescribed medication for anemia?                                                           | [C17] | not 0<br>yes 1<br>IGN 9                                                      |
| 62. Prescribed vitamins?                                                                        | [C18] | not 0<br>yes 1<br>IGN 9                                                      |
| 63. Guided about breastfeeding?                                                                 | [C19] | not 0<br>yes 1<br>IGN 9                                                      |
| 64. Asked if he was using any medication?                                                       | [C20] | not 0<br>yes 1<br>IGN 9                                                      |
| 65. Advised on the risk of using drugs without medical advice during pregnancy?                 | [C21] | not 0<br>yes 1<br>IGN 9                                                      |
| 66. Advised on exercise, like walking, for example?<br>SE NÃO88                                 | [C22] | not 0<br>yes 1<br>IGN 9                                                      |
| 67. What did they say to Mrs.?                                                                  | [C23] | I should do first<br>should reduce or change 2<br>I should not do 3<br>IGN 9 |
| 68. He examined her breasts?                                                                    | [C24] | not 0<br>yes 1<br>IGN 9                                                      |
| 69. Did examining prevention of cervical cancer?                                                | [C25] | not 0<br>yes 1<br>did before pregnancy 2<br>IGN 9                            |
| 70. During prenatal care, Mrs. made the tetanus vaccine?<br><br>IF NOT, OR ALREADY vaccinated 2 | [C26] | not 0<br>yes 1<br>had been vaccinated two<br>IGN 9                           |
| 71. How many doses of tetanus received?<br>(N = number of doses; 7 = 1 booster dose; 9 = IGN)   | [C27] | __ Doses                                                                     |

TABLE 1 - MORBIDITY CURRENT OF PREGNANCY

| During pregnancy ...                                          | 0 = Not<br>2 = yes, treaty | 1 = yes, untreated<br>9 = IGN |
|---------------------------------------------------------------|----------------------------|-------------------------------|
| 72. Mrs. had high blood pressure?                             | [C28] 0                    | 1 2 9                         |
| 73. If yes, already had high blood pressure before pregnancy? | [C29] 0                    | 1 2 9                         |
| 74. Mrs. had diabetes?                                        | [C30] 0                    | 1 2 9                         |
| 75. If yes, already had diabetes before pregnancy?            | [C31] 0                    | 1 2 9                         |
| 76. Mrs. problem had depression or nervous?                   | [C32] 0                    | 1 2 9                         |
| 77. If yes, already before pregnancy?                         | [C33] 0                    | 1 2 9                         |
| 78. Mrs. had anemia?                                          | [C34] 0                    | 1 2 9                         |
| 79. If yes, had anemia before pregnancy?                      | [C35] 0                    | 1 2 9                         |
| 80. Mrs. had threatened abortion?                             | [C36] 0                    | 1 2 9                         |
| 81. Mrs. had threatened premature labor?                      | [C37] 0                    | 1 2 9                         |
| 82. Mrs. had runny?                                           | [C38] 0                    | 1 2 9                         |
| 83. Mrs. had bleeding in the last 3 months?                   | [C39] 0                    | 1 2 9                         |
| 84. Mrs. had urinary tract infection?                         | [C40] 0                    | 1 2 9                         |
| 85. Mrs. had some other infection?                            | [C41] 0                    | 1 2 9                         |
| 86. If yes, which one? _____                                  | [C42]                      | _____                         |

|                                                                                                 |       |                                                                |
|-------------------------------------------------------------------------------------------------|-------|----------------------------------------------------------------|
| 87. Mrs. has, or ever had asthma or bronchitis?                                                 | [C43] | not 0<br>yes, one has<br>yes, we had two                       |
| 88. In the last 3 months of pregnancy, Mrs. had back pain ...<br>(Read all alternatives)        | [C44] | never 1<br>Sometimes two<br>most of time 3<br>4 where<br>IGN 9 |
| 89. In the last 3 months of pregnancy, Ms. felt sad or depressed ...<br>(Read all alternatives) | [C45] | never 1<br>Sometimes two<br>most of time 3<br>4 where<br>IGN 9 |
| 90. Mrs. ever been hospitalized during this pregnancy?<br>IF NO 94                              | [C46] | not 0<br>yes 1                                                 |
| 91. How many admissions?<br>What was the problem?                                               | [C47] | ___ Admissions                                                 |
| 92. Problem 1: _____                                                                            | [C48] | ___                                                            |
| 93. Problem 2: _____                                                                            | [C49] | ___                                                            |
| 94. Mrs used some medicine during pregnancy?<br><br>IF NO 96                                    | [C50] | not 0<br>yes 1<br>IGN 9                                        |

| BLOCK H – PHYSICAL EXAMINATION OF THE NEWBORN     |       |                    |
|---------------------------------------------------|-------|--------------------|
| 252. Sex RN                                       | [H01] | male 1<br>female 2 |
| 253. Length                                       | [H02] | ____ _ Cm          |
| 254. Head circumference                           | [H03] | ____ _ Cm          |
| 255. Chest girth                                  | [H04] | ____ _ Cm          |
| 256. Abdominal Circumference                      | [H05] | ____ _ Cm          |
| 257. Gestational age according to Dubowitz method | [H06] |                    |
| edema .....                                       |       |                    |
| skin texture .....                                |       |                    |
| skin color .....                                  |       |                    |
| transparency skin (trunk) .....                   |       |                    |
| lanugo (back) .....                               |       |                    |
| plantar furrows .....                             |       |                    |
| nipple training .....                             |       |                    |
| mammary gland .....                               |       |                    |
| ear shape .....                                   |       |                    |
| ..... consistency ear .....                       |       |                    |
| Genital .....                                     |       |                    |
| SUBTOTAL .....                                    |       |                    |
| posture .....                                     |       |                    |
| wrist flexion .....                               |       |                    |
| ..... heel flexion .....                          |       |                    |
| bending the arms back .....                       |       |                    |
| Flexural return leg .....                         |       |                    |
| popliteal angle .....                             |       |                    |
| ..... heel ear .....                              |       |                    |
| sign scarf .....                                  |       |                    |
| head position .....                               |       |                    |
| ventral suspension .....                          |       |                    |
| SUBTOTAL .....                                    |       |                    |
|                                                   |       | ____ Score         |

## Appendix V: Pelotas 3 Month Interview Form Extract (English Translation)

|                                                                                                                                                                                                       |                  |                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|----------------------------------------------|
| 131. <Criança> Already downloaded in hospital?<br>IF NO or 143 IGN                                                                                                                                    | [C96]            | not 0<br>yes 1<br>IGN 9                      |
| 132. How many times?<br>(00 = never, 99 = IGN)                                                                                                                                                        | [C97]            | ____ Times                                   |
| Why <criança> was hospitalized?                                                                                                                                                                       |                  | No. of times                                 |
| 133. Diarrhea                                                                                                                                                                                         | [C98]            | ____                                         |
| 134. Pneumonia                                                                                                                                                                                        | [C99]            | ____                                         |
| 135. Jaundice                                                                                                                                                                                         | [C100]           | ____                                         |
| 136. Another reason: _____                                                                                                                                                                            | [C101]           | ____                                         |
|                                                                                                                                                                                                       | [C102]           | CID _____                                    |
| What hospital?                                                                                                                                                                                        |                  | No. of times                                 |
| 137. Beneficence                                                                                                                                                                                      | [C103]           | ____                                         |
| 138. Santa House                                                                                                                                                                                      | [C104]           | ____                                         |
| 139. Clinics                                                                                                                                                                                          | [C105]           | ____                                         |
| 140. FAU                                                                                                                                                                                              | [C106]           | ____                                         |
| 141. Piltcher                                                                                                                                                                                         | [C107]           | ____                                         |
| 142. Other: _____                                                                                                                                                                                     | [C108]           | ____                                         |
| 143. Compared to other babies of the same age, cries <criança> more, less or the same?                                                                                                                | [C109]           | more 1<br>less than 2<br>same three<br>IGN 9 |
| 144. <Criança> Ever had colic?<br>IF NO or 147 IGN                                                                                                                                                    | [C110]           | not 0<br>yes 1<br>IGN 9                      |
| 145. How many times had colic since yesterday?<br>(00 = not at all, 99 = IGN)                                                                                                                         | [C111]           | ____ Times                                   |
| 146. What usually do when <criança> has colic?<br>0. does nada1. stomach turns<br>2nd. gives chá3. put hot compress<br>4th. Massaging 5. gives remedy<br>6th. colo7 picks. other: _____<br>Eight. NSA | [C112]<br>[C113] | 1st option ____<br>2nd option ____           |

## Appendix VI: Pelotas 48 Month Interview Form Extract (English Translation)

| The <CRIANÇA> ever had (or has)?                                                                                                                               | no = 0   | yes = 1                                                                    | IGN = 9 | How many times? | Last time?        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|----------------------------------------------------------------------------|---------|-----------------|-------------------|
| 141. Broke a bone?                                                                                                                                             | [C96] 0  | 1                                                                          | 9       | _____           | with _____ months |
| 142. Anemia?                                                                                                                                                   | [C97] 0  | 1                                                                          | 9       | _____           | with _____ months |
| 143. Skin infection?                                                                                                                                           | [C98] 0  | 1                                                                          | 9       | _____           | with _____ months |
| 144. Convulsion with fever?                                                                                                                                    | [C99] 0  | 1                                                                          | 9       | _____           | with _____ months |
| 145. Seizures without fever?                                                                                                                                   | [C100] 0 | 1                                                                          | 9       | _____           | with _____ months |
| 146. Meningitis?                                                                                                                                               | [C101] 0 | 1                                                                          | 9       | _____           | with _____ months |
| 147. Eliminated worms?                                                                                                                                         | [C102] 0 | 1                                                                          | 9       | _____           | with _____ months |
|                                                                                                                                                                |          |                                                                            |         |                 |                   |
| 148. Since completing 2 years, <CRIANÇA> been to the doctor or clinic or hospital to check for disease?<br>IF YOU DO NOT OR IGN 152                            | [C103]   | not 0<br>yes 1<br>IGN 9                                                    |         |                 |                   |
| 149. How many times did that after 2 years? ("Often" = 77, IGN = 99)                                                                                           | [C104]   | _____ Times                                                                |         |                 |                   |
| 150. How many times in the last 3 months? ("Often" = 77, IGN = 99)                                                                                             | [C105]   | _____ Times                                                                |         |                 |                   |
| 151. Reason for last visit?<br>_____<br>_____                                                                                                                  | [C106]   | _____                                                                      |         |                 |                   |
|                                                                                                                                                                |          |                                                                            |         |                 |                   |
| 152. Since completing 2 years, Mrs. <CRIANÇA> already led to consult on Emergency Municipal Emergency Department or somewhere?<br><br>IF YOU DO NOT OR IGN 153 | [C107]   | not 0<br>municipal emergency room 1<br>prompt service 2<br>3 both<br>IGN 9 |         |                 |                   |
| 153. How many times? ("Often" = 77, IGN = 99)                                                                                                                  | [C108]   | _____ Times                                                                |         |                 |                   |
| 154. Reason for last visit?<br>_____<br>_____                                                                                                                  | [C109]   | _____                                                                      |         |                 |                   |
|                                                                                                                                                                |          |                                                                            |         |                 |                   |
| 155. Since completing 2 years, Mrs. lead <CRIANÇA> tried to consult, hospitalize or vaccinate and failed?<br>IF YOU DO NOT OR IGN 157                          | [C110]   | not 0<br>yes 1<br>IGN 9                                                    |         |                 |                   |
| 156. Why?<br>_____<br>_____                                                                                                                                    | [C111]   | _____                                                                      |         |                 |                   |
|                                                                                                                                                                |          |                                                                            |         |                 |                   |
| 157. Since <CRIANÇA> completed 2 years ever in attendance at clinics or services SUS asked to pay anything?<br><br>If "0", "2" or IGN 159                      | [C112]   | not 0<br>yes 1<br>never used SUS 2<br>IGN 9                                |         |                 |                   |



## Appendix VII: Strengths and Difficulties Questionnaire

### Strengths and Difficulties Questionnaire

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months or this school year.

Child's Name .....

Male/Female

Date of Birth .....

|                                                                     | Not<br>True              | Somewhat<br>True         | Certainly<br>True        |
|---------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|
| Considerate of other people's feelings                              | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Restless, overactive, cannot stay still for long                    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Often complains of headaches, stomach-aches or sickness             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Shares readily with other children (treats, toys, pencils etc.)     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Often has temper tantrums or hot tempers                            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Rather solitary, tends to play alone                                | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Generally obedient, usually does what adults request                | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Many worries, often seems worried                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Helpful if someone is hurt, upset or feeling ill                    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Constantly fidgeting or squirming                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Has at least one good friend                                        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Often fights with other children or bullies them                    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Often unhappy, down-hearted or tearful                              | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Generally liked by other children                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Easily distracted, concentration wanders                            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Nervous or clingy in new situations, easily loses confidence        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Kind to younger children                                            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Often lies or cheats                                                | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Picked on or bullied by other children                              | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Often volunteers to help others (parents, teachers, other children) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Thinks things out before acting                                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Steals from home, school or elsewhere                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Gets on better with adults than with other children                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Many fears, easily scared                                           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Sees tasks through to the end, good attention span                  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Signature .....

Date .....

Parent/Teacher/Other (please specify:)



## Appendix VIII: ALSPAC Pregnancy Questionnaire Extracts



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### YOUR PREGNANCY

This questionnaire asks about how you are now feeling and some questions about your background, and about your plans and preparations for the baby.

Your answers are confidential. Your name will not be on the questionnaire and none of the doctors or nurses you see will know your answers.

Please answer all the questions you can. If there are any you cannot answer or do not wish to answer that is fine. Just leave them blank.

THANK YOU VERY MUCH FOR YOUR HELP

06/02/92

Recycled Paper

14

b) how many years of your life have you been vegan?

years (If less than one year put 00)

|     |                                                                                           | Yes, most of<br>the time | Yes,<br>occasionally | No, not<br>at all |
|-----|-------------------------------------------------------------------------------------------|--------------------------|----------------------|-------------------|
| C20 | Do you now feel you've<br>put on too much weight?                                         | 1                        | 2                    | 3                 |
| C21 | Do you feel uncomfort-<br>able seeing your body<br>in the mirror?                         | 1                        | 2                    | 3                 |
| C22 | Have you had a strong<br>desire to lose weight at<br>any time during this<br>pregnancy?   | 1                        | 2                    | 3                 |
| C23 | Do you feel dissatisfied<br>about your shape?                                             | 1                        | 2                    | 3                 |
| C24 | Have you experienced any<br>loss of control over<br>eating during this<br>pregnancy?      | 1                        | 2                    | 3                 |
| C25 | Are you concerned about<br>losing any extra weight<br>you've gained in this<br>pregnancy? | 1                        | 2                    | 3                 |

C26 How many days in the past month have you drunk the equivalent  
of 2 pints of beer, 4 glasses of wine or 4 pub measures of spirit?

|           |   |                   |   |
|-----------|---|-------------------|---|
| everyday  | 1 | more than 10 days | 4 |
| 5-10 days | 2 | 3-4 days          | 3 |
| 1-2 days  | 3 | none              | 0 |

C27 At present how much of the following do you usually drink in a day:

|    | At present                               | Weekday | Weekend<br>day |
|----|------------------------------------------|---------|----------------|
| a) | beer or lager<br>(half-pints)            |         |                |
| b) | wine (glasses)                           |         |                |
| c) | spirits (pub-measures)                   |         |                |
| d) | other alcoholic drinks<br>(pub measures) |         |                |

**SECTION E: YOUR ENVIRONMENT AND LIFESTYLE**

E1 a) Are you living in the same home that you were in at the start of your pregnancy?

Yes ☐ No ☐

b) If no, how many times have you moved?

c) Have you been homeless at any time during this pregnancy?

Yes ☐ No ☐

d) Have we sent this questionnaire to your correct address?

Yes ☐ No ☐

If no, please telephone Bristol 256260 or send a card with your new address, quoting your contact number

e) Are you intending to move house in the near future?

Yes ☐ No ☐

If yes, please let us know your new address on the back cover

E2 Please indicate how often during the day you are in a room or enclosed place where other people are smoking:

|                   | (i)<br>Weekdays | (ii)<br>Weekends |
|-------------------|-----------------|------------------|
| all the time      | 1               | 1                |
| more than 5 hours | 2               | 2                |
| 3-5 hours         | 3               | 3                |
| 1-2 hours         | 4               | 4                |
| less than 1 hour  | 5               | 5                |
| not at all        | 6               | 6                |

E3 How many cigarettes per day are you yourself smoking at the moment cigarettes

E4 a) Are you currently in paid work?

Yes ☐ No ☐

If yes, go to Question E5

b) Have you worked at all during this pregnancy?

Yes ☐ No ☐ If no, go to E6

c) What date did you stop work?      /    /19

d) What was the main reason?

- ill health ☐
- tiredness ☐
- company rules ☐
- to prepare for the baby ☐
- other (please describe) ☐

e) Are you now on paid maternity leave?

Yes ☐ No ☐

**SECTION F: YOUR FEELINGS**

The questions in this section ask you about your feelings and the way you behave nowadays. Please indicate the way you feel.

|     |                                                                          | Very often | Often | Not very often | Never |
|-----|--------------------------------------------------------------------------|------------|-------|----------------|-------|
| F1  | Do you feel upset for no obvious reason?                                 | 1          | 2     | 3              | 4     |
| F2  | Do you get troubled by dizziness or shortness of breath?                 | 1          | 2     | 3              | 4     |
| F3  | Have you felt as though you might faint?                                 | 1          | 2     | 3              | 4     |
| F4  | Do you feel sick or have indigestion?                                    | 1          | 2     | 3              | 4     |
| F5  | Do you feel that life is too much effort?                                | 1          | 2     | 3              | 4     |
| F6  | Do you feel uneasy and restless?                                         | 1          | 2     | 3              | 4     |
| F7  | Do you feel tingling or prickling sensations in your body, arms or legs? | 1          | 2     | 3              | 4     |
| F8  | Do you regret much of your past behaviour?                               | 1          | 2     | 3              | 4     |
| F9  | Do you sometimes feel panicky?                                           | 1          | 2     | 3              | 4     |
| F10 | Do you find that you have little or no appetite?                         | 1          | 2     | 3              | 4     |
| F11 | Do you wake unusually early in the morning?                              | 1          | 2     | 3              | 4     |
| F12 | Do you worry a lot?                                                      | 1          | 2     | 3              | 4     |
| F13 | Do you feel tired or exhausted?                                          | 1          | 2     | 3              | 4     |
| F14 | Do you experience long periods of sadness?                               | 1          | 2     | 3              | 4     |
| F15 | Do you feel strung-up inside?                                            | 1          | 2     | 3              | 4     |
| F16 | Can you get off to sleep alright?                                        | 1          | 2     | 3              | 4     |
| F17 | Do you ever have the feeling you are going to pieces?                    | 1          | 2     | 3              | 4     |
| F18 | Do you often have excessive sweating or fluttering of the heart?         | 1          | 2     | 3              | 4     |
| F19 | Do you find yourself needing to cry?                                     | 1          | 2     | 3              | 4     |
| F20 | Do you have bad dreams which upset you when you wake up?                 | 1          | 2     | 3              | 4     |
| F21 | Do you lose the ability to feel sympathy for others?                     | 1          | 2     | 3              | 4     |
| F22 | Can you think as quickly as you used                                     | 1          | 2     | 3              | 4     |

**SECTION H: EDUCATION AND OCCUPATION**

H1 What educational qualifications do you, your partner, your mother, and your father have? Please tick all that apply

|                                                                                 | (i)<br>Your<br>self      | (ii)<br>Your<br>partner  | (iii)<br>Your<br>mother* | (iv)<br>Your<br>father*  |
|---------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a) CSE or GCSE (D, E, F or G)                                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) O-level or GCSE (A, B or C)                                                  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) A-level                                                                      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Qualifications in shorthand/<br>typing/or other skills,<br>e.g. hairdressing | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e) Apprenticeship                                                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f) State enrolled nurse                                                         | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g) State registered nurse                                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h) City & Guilds intermediate<br>technical                                      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| i) City & Guilds final<br>technical                                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| j) City & Guilds full<br>technical                                              | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| k) Teaching qualification                                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| l) University degree                                                            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| m) No qualifications                                                            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| n) Qualifications not known                                                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| o) Not applicable, no such<br>person                                            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| p) Other (please describe)                                                      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

[\* by this we mean the mother figure or father figure who was mostly responsible for bringing you up]

H2 What is the present employment situation of yourself and your partner? Please tick all that apply

|                                                                     | (i)<br>Yourself          | (ii)<br>Your partner     |
|---------------------------------------------------------------------|--------------------------|--------------------------|
| a) Working for an employer full-time<br>(more than 30 hours a week) | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Working for an employer part-time<br>(one hour or more a week)   | <input type="checkbox"/> | <input type="checkbox"/> |
| c) Self-employed, employing other<br>people                         | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Self-employed, not employing<br>other people                     | <input type="checkbox"/> | <input type="checkbox"/> |
| e) On a government employment or<br>training scheme                 | <input type="checkbox"/> | <input type="checkbox"/> |
| f) Waiting to start a job already<br>accepted                       | <input type="checkbox"/> | <input type="checkbox"/> |
| g) Unemployed and looking for a<br>job                              | <input type="checkbox"/> | <input type="checkbox"/> |
| h) At school or in other full-time<br>education                     | <input type="checkbox"/> | <input type="checkbox"/> |
| i) Unable to work because of long-<br>term sickness or disability   | <input type="checkbox"/> | <input type="checkbox"/> |

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|    |                         |                   |                       |                       |
|----|-------------------------|-------------------|-----------------------|-----------------------|
| d) | your family background  | 1                 | 2                     | 3                     |
| e) | the way you speak       | 1<br>Yes<br>often | 2<br>Yes<br>sometimes | 3<br>No not<br>at all |
| f) | your religion           | 1                 | 2                     | 3                     |
| g) | other (please describe) | 1                 | 2                     | 3                     |

|                                                                                                |                 |                 |                       |                      |
|------------------------------------------------------------------------------------------------|-----------------|-----------------|-----------------------|----------------------|
| H8 How would you describe the race or ethnic group of yourself, your partner and your parents? |                 |                 |                       |                      |
|                                                                                                | (i)<br>Yourself | (ii)<br>Partner | (iii)<br>Your mother* | (iv)<br>Your father* |
| white                                                                                          | 01              | 01              | 01                    | 01                   |
| black/Caribbean                                                                                | 02              | 02              | 02                    | 02                   |
| black/African                                                                                  | 03              | 03              | 03                    | 03                   |
| black/other<br>(please describe below)                                                         | 04              | 04              | 04                    | 04                   |
| Indian                                                                                         | 05              | 05              | 05                    | 05                   |
| Pakistani                                                                                      | 06              | 06              | 06                    | 06                   |
| Bangladeshi                                                                                    | 07              | 07              | 07                    | 07                   |
| Chinese                                                                                        | 08              | 08              | 08                    | 08                   |
| any other ethnic group<br>(please describe)                                                    | 09              | 09              | 09                    | 09                   |

(\*by this we mean the mother or father figure who was mostly responsible for bringing you up)

## Appendix IX: ALSPAC Neonatal Questionnaire Extracts

Questionnaire No:

|  |  |  |  |  |  |  |  |  |
|--|--|--|--|--|--|--|--|--|
|  |  |  |  |  |  |  |  |  |
|--|--|--|--|--|--|--|--|--|

### ME AND MY BABY

This questionnaire asks you how you are feeling, whether you are getting enough sleep and how you reacted to the actual birth of your baby.

All the answers you give are confidential. Your name and address will not be on the questionnaire.

We would be grateful if you would help us by answering as many of these questions as possible but if there is any question you do not want to answer that is fine. Just leave it blank.

THANK YOU VERY MUCH FOR YOUR HELP

06/02/92

*Recycled Paper*

A8. e) Did you have a caesarean section?

Yes after  
being in  
labour

No

Yes and  
never had  
any labour

→ If yes to this go  
to A16 on page 7

A9. How was the pain?

|                               | in labour            | during delivery      |
|-------------------------------|----------------------|----------------------|
| worse than I expected         | <input type="text"/> | <input type="text"/> |
| what I had expected           | <input type="text"/> | <input type="text"/> |
| better than I expected        | <input type="text"/> | <input type="text"/> |
| did not feel any pain         | <input type="text"/> | <input type="text"/> |
| I did not know what to expect | <input type="text"/> | <input type="text"/> |
| other (please describe)       | <input type="text"/> | <input type="text"/> |

.....

A10. Were you able to get into the positions that were most comfortable for you during labour and delivery?

|                       | in labour            | during delivery      |
|-----------------------|----------------------|----------------------|
| no, hardly at all     | <input type="text"/> | <input type="text"/> |
| yes, some of the time | <input type="text"/> | <input type="text"/> |
| yes, all of the time  | <input type="text"/> | <input type="text"/> |

A11. In the first stage of labour what was your position?

|                               | All the<br>time      | Most of<br>time      | Sometimes            | Never                |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| a) lying                      | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| b) sitting                    | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| c) standing/walking           | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| d) other<br>(please describe) | <input type="text"/> | <input type="text"/> | <input type="text"/> |                      |

For office use

|  |  |
|--|--|
|  |  |
|--|--|



B10. How often have you drunk alcoholic drinks? Please indicate for each of the following times:

|                               | Not at all                     | Less than once a week          | At least once a week           | 1-2 glasses every day          | At least 3-9 glasses every day | At least 10 glasses every day  |
|-------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| a) Last 2 months of pregnancy | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> | <input type="text" value="4"/> | <input type="text" value="5"/> | <input type="text" value="6"/> |
| b) Since you had the baby     | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> | <input type="text" value="4"/> | <input type="text" value="5"/> | <input type="text" value="6"/> |

[By glass we mean a pub measure of spirits, half a pint of lager or cider, a wine glass of wine, etc]

c) How many days in the past month have you drunk the equivalent of 2 pints of beer, 4 glasses of wine or 4 pub measures of spirit?

|           |                                |                   |                                |
|-----------|--------------------------------|-------------------|--------------------------------|
| everyday  | <input type="text" value="5"/> | more than 10 days | <input type="text" value="4"/> |
| 5-10 days | <input type="text" value="3"/> | 3-4 days          | <input type="text" value="2"/> |
| 1-2 days  | <input type="text" value="1"/> | none              | <input type="text" value="0"/> |

B11. a) Did you attend antenatal or parentcraft classes during your pregnancy?

Yes  No  → If no, go to Section C on page 14

If yes,

b) were they run by the:

|                                             | Yes                            | No                             |
|---------------------------------------------|--------------------------------|--------------------------------|
| i) hospital                                 | <input type="text" value="1"/> | <input type="text" value="2"/> |
| ii) health centre or local antenatal clinic | <input type="text" value="1"/> | <input type="text" value="2"/> |
| iii) NCT (National Childbirth Trust)        | <input type="text" value="1"/> | <input type="text" value="2"/> |
| iv) other (please describe)                 | <input type="text" value="1"/> | <input type="text" value="2"/> |

.....

c) how many times did you go?  times

d) did your partner ever go with you?

Yes  No

For office use

## Appendix X: INTER-NDA

| The INTERGROWTH-21 <sup>st</sup> Neurodevelopment Assessment (INTER-NDA) |                                                                                                                                                                                            |                                                      |                                                                  |                                                                   |                                    |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------------------------|------------------------------------|
| No.                                                                      | Item                                                                                                                                                                                       | Observed performance                                 |                                                                  |                                                                   |                                    |
| 1                                                                        | Builds a tower of 5 cubes (trials =3, demonstration =3)                                                                                                                                    | 5 cubes                                              | 3–4 cubes                                                        | 2 cubes                                                           | No attempt                         |
| 2                                                                        | Names 4 colors when asked to do so (trials =0)                                                                                                                                             | Names 4 colors                                       | Names 3 colors                                                   | Names 1 or 2 colors                                               | Does not name any color            |
| 3                                                                        | Matches 3 cubes of same colors when requested to do so (trials =1, demonstration =1 of one color)                                                                                          | Matches 3 colors                                     | Matches 2 colors                                                 | Matches 1 color                                                   | Does not match any color           |
| 4                                                                        | Hands the examiner one cube when asked to do so (Examiner says "Please give me one cube" & keeps palm open for 5 seconds after child has handed over 1 cube; trials =1)                    | Hands only one block within 5 seconds                | Hands only one block in more than 5 seconds                      | Hands two or more blocks                                          | Does not hand any block/No attempt |
| 5                                                                        | Puts the spoon in the cup when asked to do so (trials =5)                                                                                                                                  | Puts the spoon in cup in ≤3 trials                   | Puts the spoon in cup in ≤3 trials in 4–5 trials                 | Takes the spoon or the cup but does not complete action           | No attempt                         |
| 6                                                                        | Matches shapes on board (trials =5, demonstration =1 if 1 <sup>st</sup> trial unsuccessful)                                                                                                | All shapes in ≤3 trials                              | All shapes with repeated demonstration i.e. 4–5 trials           | One or two shapes 4–5 trials                                      | No attempt                         |
| 7                                                                        | Matches shapes on rotated board (trials =5, demonstration =1 if 1 <sup>st</sup> trial unsuccessful)                                                                                        | All shapes in ≤3 trials                              | All shapes with repeated demonstration i.e. 4–5 trials           | One or two shapes 4–5 trials                                      | No attempt                         |
| 8                                                                        | Points correctly when asked "Where is the door/entrance to the room?" (trials =5)                                                                                                          | Identifies door correctly in ≤3 trials               | Identifies door correctly in 4–5 trials                          | Attempts, but does not identify door                              | No attempt                         |
| 9                                                                        | Puts a raisin precisely inside a small opening in a bottle (trials =1, demonstration =1; test both hands)                                                                                  | Precise release of raisin into bottle with each hand | Clumsy release, raisin falls out of bottle with one or more hand | Attempts but unsuccessful release with one or more hand           | No attempt                         |
| 10                                                                       | Drinks water from cup/sippy cup when placed in front of child (trials =1, maternal report if sippy cup unavailable)                                                                        | Drinks in a well-coordinated manner without spilling | Drinks clumsily & spills                                         | Attempts but unsuccessful                                         | No attempt                         |
| 11                                                                       | Looks towards an object located across the room when pointed at by the examiner (trials =5)                                                                                                | Looks or points at object in ≤3 trials               | Looks or points at object in 4–5 trials                          | Looks at the wrong object, or attempts but cannot identify object | No attempt                         |
| 12                                                                       | Pretends to drink from the cup when a cup is placed in front of him/her (trials =1, demonstration =1)                                                                                      | Spontaneous                                          | After 1 demonstration                                            | Partial attempt after 1 demonstration                             | No attempt                         |
| 13                                                                       | Able to make a cup of tea with the toy tea set when requested by examiner (Examiner says "Can you make a cup of tea?") (trials =2, demonstration =1 if 1 <sup>st</sup> trial unsuccessful) | Spontaneous                                          | After 1 demonstration                                            | Partial attempt                                                   | No attempt                         |
| 14                                                                       | Feeds doll when requested to (Examiner says "Can you give the dolly some tea?") (trials =2, demonstration =1 if 1 <sup>st</sup> trial unsuccessful)                                        | Spontaneous                                          | After 1 demonstration                                            | Partial attempt after 1 demonstration                             | No attempt                         |

| The INTERGROWTH-21 <sup>st</sup> Neurodevelopment Assessment (INTER-NDA)                  |                                                                                                   |                                                             |                                                         |                                                           |                                      |
|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------|-----------------------------------------------------------|--------------------------------------|
| No.                                                                                       | Item                                                                                              | Observed performance                                        |                                                         |                                                           |                                      |
| 15                                                                                        | Imitates straight scribe (trials =5, demonstration =5)                                            | ≤3 trials                                                   | 4–5 trials; with difficulty                             | Attempts (hold crayon)                                    | Cannot hold crayon                   |
| 16                                                                                        | Identifies glitter bracelet under correct washcloth (trials =5, test both sides)                  | Finds bracelet correctly in ≤2 trials on both sides         | Find bracelet correctly in 3 trials or on one side only | Find bracelet correctly in 4–5 trials or on one side only | Does not find bracelet or no attempt |
| 17                                                                                        | Correctly identifies object groups using plurals                                                  | Uses 5 plurals                                              | Uses 3–4 plurals                                        | Identifies 1–2 plurals                                    | Does not use any plurals             |
| 18                                                                                        | Asks for toilet by gesture or verbally ( <i>maternal report</i> )                                 | Always                                                      | Occasionally                                            | Partial (only for bowel movement)                         | Never                                |
| 19                                                                                        | Runs ( <i>maternal report</i> )                                                                   | Runs steadily                                               | Attempts                                                | Walks only                                                | Walks with support                   |
| 20                                                                                        | Throws a ball very near (trials =1, demonstration =1, test both sides)                            | Good release                                                | Unsteady release                                        | Attempts                                                  | No attempt                           |
| 21                                                                                        | Kicks ball ( <i>maternal report</i> )                                                             | Kicks ball with flexed                                      | Attempts                                                | Walks only                                                | No attempt                           |
| 22                                                                                        | Climbs upstairs holding rail, 2 feet/stair or in adult fashion ( <i>maternal report</i> )         | Climbs stairs alone holding rail                            | Unsteady                                                | Needs help                                                | No attempt                           |
| 23                                                                                        | Uses 2–4 syllable babble such as dada, mama but not specifically to anything or any person        | Spontaneously                                               | Mimics                                                  | 1 syllable babble e.g. ba, ma, da                         | None                                 |
| 24                                                                                        | Use two words together                                                                            | Yes, appropriate use                                        | Yes, in appropriate use                                 | One word                                                  | No attempt                           |
| 25                                                                                        | Indicates by gesture to say no ( <i>maternal report if not observed during assessment</i> )       | Indicates in ≤3 trials                                      | Indicates in 4–5 trials                                 | Attempts, but incomplete indication                       | No attempt                           |
| 26                                                                                        | Use of a pronoun e.g. me, my, she, he, it, I                                                      | Correct use                                                 | Incorrect use                                           | No use                                                    | No use                               |
| 27                                                                                        | How many words does the child use during the assessment other than mama/dada                      | ≥8 words                                                    | 6–7 words                                               | 4–5 words                                                 | ≤3 words                             |
| 28                                                                                        | How many sentences of 3 words or more does the child use during the assessment?                   | ≥2                                                          | 1                                                       | Only two – one word utterances                            | None                                 |
| 29                                                                                        | In how many instances does the child follow on a topic of conversation providing new information? | At least one, using ≥2 words, providing correct information | Uses single words, provides correct information         | Uses any number of words, provides incorrect information  | Does not follow up on conversations  |
| 30                                                                                        | Combines word and gesture when asked (trials =1, do not demonstrate)                              | Yes, appropriate use & completed gesture                    | Yes, inappropriate use but complete gesture             | Incomplete gesture and inappropriate use                  | None                                 |
| What is the child's native (first) language?                                              |                                                                                                   |                                                             |                                                         |                                                           |                                      |
| What is the language in which the assessment is being conducted?                          |                                                                                                   |                                                             |                                                         |                                                           |                                      |
| Does the child speak/understand any languages other than his/her native (first) language? |                                                                                                   |                                                             |                                                         |                                                           |                                      |
| How often were the following behaviors in the child during the assessment?                |                                                                                                   |                                                             |                                                         |                                                           |                                      |
| 31                                                                                        | Positive Affect                                                                                   | Never or rarely                                             | Some of the time                                        | Most of the time                                          |                                      |

| The INTERGROWTH-21 <sup>st</sup> Neurodevelopment Assessment (INTER-NDA)                                                       |                                                 |                      |                  |                  |
|--------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|----------------------|------------------|------------------|
| No.                                                                                                                            | Item                                            | Observed performance |                  |                  |
| 32                                                                                                                             | Exploration                                     | Never or rarely      | Some of the time | Most of the time |
| 33                                                                                                                             | Ease of engagement                              | Never or rarely      | Some of the time | Most of the time |
| 34                                                                                                                             | Cooperativeness                                 | Never or rarely      | Some of the time | Most of the time |
| 35                                                                                                                             | Adaptability to change                          | Never or rarely      | Some of the time | Most of the time |
| 36                                                                                                                             | Distractibility                                 | Never or rarely      | Some of the time | Most of the time |
| 37                                                                                                                             | Negative affect                                 | Never or rarely      | Some of the time | Most of the time |
| <b>Caregiver Reported Child Behaviour Questionnaire</b>                                                                        |                                                 |                      |                  |                  |
| Instructions to caregiver: Please fill in this form to reflect your view of your child's behavior, even if others do not agree |                                                 |                      |                  |                  |
| 38                                                                                                                             | Likes playing with other children               | Not true             | Sometimes true   | Often true       |
| 39                                                                                                                             | Can't concentrate, can't pay attention for long | Not true             | Sometimes true   | Often true       |
| 40                                                                                                                             | Can't sit still, restless or hyperactive        | Not true             | Sometimes true   | Often true       |
| 41                                                                                                                             | Disturbed by any change in routine              | Not true             | Sometimes true   | Often true       |
| 42                                                                                                                             | Nervous movements or twitching                  | Not true             | Sometimes true   | Often true       |
| 43                                                                                                                             | Shows panic for no good reason                  | Not true             | Sometimes true   | Often true       |
| 44                                                                                                                             | Poorly coordinated or clumsy                    | Not true             | Sometimes true   | Often true       |
| 45                                                                                                                             | Quickly shifts from one activity to another     | Not true             | Sometimes true   | Often true       |
| 46                                                                                                                             | Rapid shifts between sadness and excitement     | Not true             | Sometimes true   | Often true       |
| 47                                                                                                                             | Sudden changes in mood or feelings              | Not true             | Sometimes true   | Often true       |
| 48                                                                                                                             | Sulks a lot                                     | Not true             | Sometimes true   | Often true       |
| 49                                                                                                                             | Upset by new people or situations               | Not true             | Sometimes true   | Often true       |
| 50                                                                                                                             | Wanders away                                    | Not true             | Sometimes true   | Often true       |
| 51                                                                                                                             | Whining                                         | Not true             | Sometimes true   | Often true       |
| 52                                                                                                                             | Worries                                         | Not true             | Sometimes true   | Often true       |
| 53                                                                                                                             | Responds well to affection                      | Not true             | Sometimes true   | Often true       |
| <b>END</b>                                                                                                                     |                                                 |                      |                  |                  |

## Appendix XI: Child Behaviour Questionnaire (CBQ; English Version)

|                                                                                   |                                                                                                |                           |
|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|---------------------------|
|  | <b>Postnatal Infant Follow-up Study - 2 year visit</b><br><b>Child Behaviour Questionnaire</b> | <b>CBQ</b><br>Page 1 of 1 |
|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|---------------------------|

|                                                          |                                                                                                                                                      |
|----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| FGLS Number <input type="text"/> - <input type="text"/>  | Date of birth <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>      |
| Paediatric Outpatient Record Number <input type="text"/> | Date of this visit <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> |
| Paediatric Hospital Record Number <input type="text"/>   | Was the child part of the Preterm Postnatal Follow-up <input type="checkbox"/> yes <input type="checkbox"/> no                                       |

**Instructions:**

Please fill out this form to reflect **your** view of your child's behaviour, even if other people might not agree.  
 Feel free to write additional comments beside each item. **Be sure to answer all questions.**

|                                                    | <i>Not True</i> | <i>Sometimes</i> | <i>Often True</i> |
|----------------------------------------------------|-----------------|------------------|-------------------|
| 1. Likes playing with other children               | 0               | 1                | 2                 |
| 2. Can't concentrate, can't pay attention for long | 0               | 1                | 2                 |
| 3. Can't sit still, restless, or hyperactive       | 0               | 1                | 2                 |
| 4. Disturbed by any change in routine              | 0               | 1                | 2                 |
| 5. Nervous movements or twitching                  | 0               | 1                | 2                 |
| 6. Shows panic for no good reason                  | 0               | 1                | 2                 |
| 7. Poorly coordinated or clumsy                    | 0               | 1                | 2                 |
| 8. Quickly shifts from one activity to another     | 0               | 1                | 2                 |
| 9. Rapid shifts between sadness and excitement     | 0               | 1                | 2                 |
| 10. Sudden changes in mood or feelings             | 0               | 1                | 2                 |
| 11. Sulks a lot                                    | 0               | 1                | 2                 |
| 12. Upset by new people or situations              | 0               | 1                | 2                 |
| 13. Wanders away                                   | 0               | 1                | 2                 |
| 14. Whining                                        | 0               | 1                | 2                 |
| 15. Worries                                        | 0               | 1                | 2                 |
| 16. Responds well to affection                     | 0               | 1                | 2                 |

|                         |                                           |
|-------------------------|-------------------------------------------|
| Signature of Researcher | <input style="width: 95%;" type="text"/>  |
| Researcher Code         | <input type="text"/> <input type="text"/> |





## Appendix XIII: INTERGROWTH-21<sup>st</sup> Delivery Form

|                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>INTERGROWTH-21<sup>ST</sup></b><br><br>UNIVERSITY OF<br><b>OXFORD</b>                                                                                                                                                                                                                                                                                                                                   | <b>NEWBORN CROSS SECTIONAL STUDY</b><br><b>FETAL GROWTH LONGITUDINAL STUDY</b><br><b>Pregnancy and Delivery</b>                                         | <b>DEV</b><br>Page 1 of 5                                                                                                                                                                                                                                                                                                                                                             |
| Study Subject Number <span style="border: 1px solid black; padding: 2px;">0</span> <span style="border: 1px solid black; padding: 2px;">7</span> - <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> |                                                                                                                                                         | Study Hospital Code <span style="border: 1px solid black; padding: 2px;">0</span> <span style="border: 1px solid black; padding: 2px;">7</span> - <span style="border: 1px solid black; padding: 2px;">1</span>                                                                                                                                                                       |
| Please answer all yes/no questions by placing an 'x' in the corresponding box                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                       |
| 1. Is the woman part of the Fetal Growth Longitudinal Study?                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                         | yes <input type="checkbox"/> no <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                              |
| 2. If yes, please obtain the Study Subject Number for the Fetal Growth Longitudinal Study and alert the study coordinator                                                                                                                                                                                                                                                                                  |                                                                                                                                                         | <span style="border: 1px solid black; padding: 2px;">0</span> <span style="border: 1px solid black; padding: 2px;">7</span> - <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> |
| <b>Section 1: Demographic, socioeconomic and nutritional characteristics</b>                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                       |
| 3. Age                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                         | <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span>                                                                                                                                                                                                                                                           |
| 4. Maternal height (cm)                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                         | <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> . <span style="border: 1px solid black; padding: 2px;"> </span> cm                                                            |
| 5. 1st trimester or pre-pregnancy weight (kg)                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                         | <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span> . <span style="border: 1px solid black; padding: 2px;"> </span> kg                                                            |
| 6. Has she smoked/chewed tobacco during this pregnancy?                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                         | yes <input type="checkbox"/> no <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                              |
| 7. if she smoked cigarettes, how many per day?                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                         | <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span>                                                                                                                                                                                                                                                           |
| 8. Has she used any recreational drugs during this pregnancy?                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                         | yes <input type="checkbox"/> no <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                              |
| 9. Has she had 5 or more units of alcohol per week, on average, during this pregnancy?<br>(1 unit = small glass (125ml) of wine or one bottle/can (330ml) of beer)                                                                                                                                                                                                                                         |                                                                                                                                                         | yes <input type="checkbox"/> no <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                              |
| 10. Has she been involved in any high risk occupation and/or vigorous or contact sport during her pregnancy?<br>(see table)                                                                                                                                                                                                                                                                                |                                                                                                                                                         | yes <input type="checkbox"/> no <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                              |
| 11. Has she followed any special diets during her pregnancy e.g. vegetarian with no animal products, weight loss programme, malabsorption treatment, gluten-free diet? (see table)                                                                                                                                                                                                                         |                                                                                                                                                         | yes <input type="checkbox"/> no <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                              |
| 12. Country specific; see attached sheet                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                         | yes <input type="checkbox"/> no <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                              |
| 13. Current marital status (please cross one box only)                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                         | Single <input type="checkbox"/> Widowed <input type="checkbox"/><br>Married/Cohabiting <input type="checkbox"/> Separated/Divorced <input type="checkbox"/>                                                                                                                                                                                                                           |
| 14. Total number of years of formal education                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                         | <span style="border: 1px solid black; padding: 2px;"> </span> <span style="border: 1px solid black; padding: 2px;"> </span>                                                                                                                                                                                                                                                           |
| 15. Highest level of education she attended? (please cross one box only)                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                         | Primary <input type="checkbox"/> Professional/ technical training <input type="checkbox"/><br>Secondary <input type="checkbox"/> University <input type="checkbox"/>                                                                                                                                                                                                                  |
| 16. Which of the following best describes her occupational status?<br>(please cross one box only)                                                                                                                                                                                                                                                                                                          |                                                                                                                                                         | Housework <input type="checkbox"/> Skilled manual work <input type="checkbox"/><br>Manager/professional/technical <input type="checkbox"/> Unskilled manual work <input type="checkbox"/><br>Clerical support, service or sales <input type="checkbox"/> Other <input type="checkbox"/>                                                                                               |
| <b>Section 2: Medical history</b>                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                       |
| Prior to this pregnancy, was she diagnosed with, or treated for any of the following medical conditions? (cross all that apply)                                                                                                                                                                                                                                                                            |                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                       |
| 17. Diabetes <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                                                                                                                                      | 26. Any hematologic condition including sickle-cell anaemia or leukaemia <input type="checkbox"/> yes <input type="checkbox"/> no                       |                                                                                                                                                                                                                                                                                                                                                                                       |
| 18. Thyroid disease <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                                                                                                                               | 27. Epilepsy <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                       |
| 19. Other endocrinological conditions <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                                                                                                             | 28. HIV or AIDS <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                |                                                                                                                                                                                                                                                                                                                                                                                       |
| 20. Cardiac disease <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                                                                                                                               | 29. Malaria <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                       |
| 21. Hypertension/chronic hypertension <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                                                                                                             | 30. Tuberculosis <input type="checkbox"/> yes <input type="checkbox"/> no                                                                               |                                                                                                                                                                                                                                                                                                                                                                                       |
| 22. Chronic respiratory disease (including chronic asthma) <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                                                                                        | 31. Crohn's disease, coeliac disease, ulcerative colitis or any severe malabsorption condition <input type="checkbox"/> yes <input type="checkbox"/> no |                                                                                                                                                                                                                                                                                                                                                                                       |
| 23. Proteinuria, kidney disease or chronic renal disease <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                                                                                          | 32. Any congenital abnormality <input type="checkbox"/> yes <input type="checkbox"/> no                                                                 |                                                                                                                                                                                                                                                                                                                                                                                       |
| 24. Any type of malignancy/cancer <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                                                                                                                 | 33. Other clinically relevant condition <input type="checkbox"/> yes <input type="checkbox"/> no                                                        |                                                                                                                                                                                                                                                                                                                                                                                       |
| 25. Lupus erythematosus <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                       |

|                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
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| Study Subject Number <span style="border: 1px solid black; padding: 0 5px;">0</span> <span style="border: 1px solid black; padding: 0 5px;">7</span> — <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span> |                                                                                                                                                                                                                                                                            | Study Hospital Code <span style="border: 1px solid black; padding: 0 5px;">0</span> <span style="border: 1px solid black; padding: 0 5px;">7</span> — <span style="border: 1px solid black; padding: 0 5px;">1</span>                                                                                                                                                                               |                                                          |
| <b>Section 3: Gynaecological history</b>                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 34. Did she have regular (24-32 day) menstrual cycles in the 3 months prior to her pregnancy?                                                                                                                                                                                                                                                                                                                          | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 35. Has she used hormonal contraceptives or been breastfeeding in the 2 months prior to her current pregnancy?                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 36. Was this pregnancy conceived with fertility treatment?                                                                                                                                                                                                                                                                                                                                                             | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 37. First day of the last menstrual period (LMP)                                                                                                                                                                                                                                                                                                                                                                       | Date                                                                                                                                                                                                                                                                       | <span style="border: 1px solid black; padding: 0 5px;">D</span> <span style="border: 1px solid black; padding: 0 5px;">D</span> — <span style="border: 1px solid black; padding: 0 5px;">M</span> <span style="border: 1px solid black; padding: 0 5px;">M</span> — <span style="border: 1px solid black; padding: 0 5px;">Y</span> <span style="border: 1px solid black; padding: 0 5px;">Y</span> |                                                          |
| 38. Was she certain of her date of LMP?                                                                                                                                                                                                                                                                                                                                                                                | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 39. Date of the <u>first</u> ultrasound scan during this pregnancy                                                                                                                                                                                                                                                                                                                                                     | Date                                                                                                                                                                                                                                                                       | <span style="border: 1px solid black; padding: 0 5px;">D</span> <span style="border: 1px solid black; padding: 0 5px;">D</span> — <span style="border: 1px solid black; padding: 0 5px;">M</span> <span style="border: 1px solid black; padding: 0 5px;">M</span> — <span style="border: 1px solid black; padding: 0 5px;">Y</span> <span style="border: 1px solid black; padding: 0 5px;">Y</span> |                                                          |
| 40. What was the CRL(crown rump length) measurement at the <u>first</u> ultrasound scan?                                                                                                                                                                                                                                                                                                                               | <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span> mm         |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 41. What was the BPD(biparietal diameter) measurement at the <u>first</u> ultrasound scan?                                                                                                                                                                                                                                                                                                                             | <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span> mm         |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 42. Estimated gestational age at the <u>first</u> ultrasound scan                                                                                                                                                                                                                                                                                                                                                      | <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span> Weeks <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span> Days |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| <b>Section 4: Obstetric history</b>                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 43. Number of previous pregnancies, excluding the present pregnancy (if 0, skip to Section 5)                                                                                                                                                                                                                                                                                                                          | <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span>                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 44. Have her last two pregnancies before this one ended in miscarriage?                                                                                                                                                                                                                                                                                                                                                | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 45. How many previous births has she had, excluding this birth (if 0, skip to Section 5)?                                                                                                                                                                                                                                                                                                                              | <span style="border: 1px solid black; padding: 0 5px;"> </span> <span style="border: 1px solid black; padding: 0 5px;"> </span>                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 46. Have ANY of her other babies weighed less than 2.5kg or more than 4.5kg?                                                                                                                                                                                                                                                                                                                                           | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 47. Have ANY of her other babies been born preterm (<37 weeks gestation)?                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 48. Has she had ANY previous stillbirths or neonatal deaths?                                                                                                                                                                                                                                                                                                                                                           | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| <b>Section 5: Clinical conditions</b>                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| During this pregnancy was she diagnosed with, or treated for, any of the following conditions (cross all that apply)                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |
| 49. Cardiac disease                                                                                                                                                                                                                                                                                                                                                                                                    | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   | 57. Respiratory tract infection requiring antibiotic/antiviral treatment                                                                                                                                                                                                                                                                                                                            | <input type="checkbox"/> yes <input type="checkbox"/> no |
| 50. Chronic respiratory disease (including chronic asthma)                                                                                                                                                                                                                                                                                                                                                             | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   | 58. Any other infection requiring antibiotic/antiviral treatment                                                                                                                                                                                                                                                                                                                                    | <input type="checkbox"/> yes <input type="checkbox"/> no |
| 51. Malaria                                                                                                                                                                                                                                                                                                                                                                                                            | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   | 59. Positive syphilis test                                                                                                                                                                                                                                                                                                                                                                          | <input type="checkbox"/> yes <input type="checkbox"/> no |
| 52. Mental illness e.g. depression                                                                                                                                                                                                                                                                                                                                                                                     | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   | 60. HIV or AIDS                                                                                                                                                                                                                                                                                                                                                                                     | <input type="checkbox"/> yes <input type="checkbox"/> no |
| 53. Epilepsy                                                                                                                                                                                                                                                                                                                                                                                                           | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   | 61. Any sexually transmitted infection                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> yes <input type="checkbox"/> no |
| 54. Thyroid disease or any other endocrinological condition                                                                                                                                                                                                                                                                                                                                                            | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   | 62. Any type of malignancy or cancer                                                                                                                                                                                                                                                                                                                                                                | <input type="checkbox"/> yes <input type="checkbox"/> no |
| 55. Lower urinary tract infection requiring antibiotic treatment                                                                                                                                                                                                                                                                                                                                                       | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   | 63. Any other medical/surgical condition requiring treatment or referral                                                                                                                                                                                                                                                                                                                            | <input type="checkbox"/> yes <input type="checkbox"/> no |
| 56. Pyelonephritis                                                                                                                                                                                                                                                                                                                                                                                                     | <input type="checkbox"/> yes <input type="checkbox"/> no                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                     |                                                          |



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| <b>INTERGROWTH-21ST</b><br><br>UNIVERSITY OF<br><b>OXFORD</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>NEWBORN CROSS SECTIONAL STUDY</b><br><b>FETAL GROWTH LONGITUDINAL STUDY</b><br><b>Pregnancy and Delivery</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>DEV</b><br>Page 3 of 5 |
| Study Subject Number <span style="border: 1px solid black; padding: 2px 5px;">0</span> <span style="border: 1px solid black; padding: 2px 5px;">7</span> - <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| Study Hospital Code <span style="border: 1px solid black; padding: 2px 5px;">0</span> <span style="border: 1px solid black; padding: 2px 5px;">7</span> - <span style="border: 1px solid black; padding: 2px 5px;">1</span>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| <b>Section 6: Pregnancy related complications</b><br>During this pregnancy was she diagnosed with, or treated for, any of the following conditions (cross all that apply)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| 64. Severe vomiting requiring hospitalisation <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>65. Gestational diabetes <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>66. Vaginal bleeding before 15 weeks <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>67. Vaginal bleeding at 15-27 weeks <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>68. Vaginal bleeding after 27 weeks <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>69. Pregnancy-induced hypertension <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>70. Preeclampsia <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span>                                                                                                                                                                                                                                                                                                                                                 | 71. Severe preeclampsia/Eclampsia/HELLP syndrome <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>72. Rhesus disease <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>73. Preterm labour <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>74. Fetal distress <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>75. Suspected impaired fetal growth or small for gestational age <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>76. Any other pregnancy related condition requiring treatment or referral <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                           |
| 77. Lowest haemoglobin level (if available) <span style="float: right;">&lt;15 weeks <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> g/dl</span> <span style="float: right;">15-27 weeks <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> g/dl</span> <span style="float: right;">&gt;27 weeks <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> g/dl</span>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| <b>Section 7: Nutritional supplements / Medications</b><br>During this pregnancy, has she routinely taken any of the following supplements?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| 78. Iron <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>79. Folic acid <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>80. Calcium <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 81. Food supplements <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>82. Multi-vitamins/minerals <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                           |
| During this pregnancy, has she taken any of the following medications?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| 83. Routine aspirin <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>84. Any antibiotics or antivirals (except those used for PROM) <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>85. Antibiotics used for PROM <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>86. Non-steroidal anti-inflammatories <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 87. Insulin <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>88. Prophylactic steroids for preterm labour <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>89. Any other treatment <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                           |
| <b>Section 8: Delivery</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| 90. Onset of labour (cross one box only)<br>Spontaneous <input type="checkbox"/> Induced <input type="checkbox"/> No Labour <input type="checkbox"/><br>91. Did she have pre-labour rupture of membranes (PROM)? <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 92. Mode of delivery (cross one box only)<br>Vaginal spontaneous <input type="checkbox"/> Assisted breech or breech extraction <input type="checkbox"/><br>Vaginal assisted (e.g. forceps, vacuum) <input type="checkbox"/> Caesarean section <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                           |
| If labour was induced or a caesarean section was performed please cross all indications that apply                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                           |
| 93. Vaginal bleeding <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>94. Fetal death <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>95. Pregnancy-induced hypertension <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>96. Preeclampsia <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>97. Severe preeclampsia/Eclampsia/HELLP Syndrome <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>98. Breech presentation <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>99. Fetal distress <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>100. Failure to progress <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>101. Cephalo-pelvic disproportion <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>102. Prelabour rupture of membranes (PROM) <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span> | 103. Suspected impaired fetal growth or small for gestational age <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>104. Post term (>42 weeks gestation) <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>105. Rhesus disease <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>106. HIV or AIDS <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>107. Any sexually transmitted infections <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>108. Any infections requiring antibiotic/antiviral treatment <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>109. Maternal request <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>110. Any other maternal reason <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>111. Any other fetal reason <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span><br>112. Previous caesarean section <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span> |                           |

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| <b>INTERGROWTH-21ST</b><br><br><b>UNIVERSITY OF OXFORD</b> | <b>NEWBORN CROSS SECTIONAL STUDY</b><br><b>FETAL GROWTH LONGITUDINAL STUDY</b><br><b>Pregnancy and Delivery</b> | <b>DEV</b><br>Page 4 of 5 |
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| Study Subject Number <span style="border: 1px solid black; padding: 2px 5px;">0</span> <span style="border: 1px solid black; padding: 2px 5px;">7</span> - <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> | Study Hospital Code <span style="border: 1px solid black; padding: 2px 5px;">0</span> <span style="border: 1px solid black; padding: 2px 5px;">7</span> - <span style="border: 1px solid black; padding: 2px 5px;">1</span> |
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**Section 9: Newborn outcomes and care**

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| 113. Date of delivery <span style="border: 1px solid black; padding: 2px 5px;">D</span> <span style="border: 1px solid black; padding: 2px 5px;">D</span> - <span style="border: 1px solid black; padding: 2px 5px;">M</span> <span style="border: 1px solid black; padding: 2px 5px;">M</span> - <span style="border: 1px solid black; padding: 2px 5px;">Y</span> <span style="border: 1px solid black; padding: 2px 5px;">Y</span><br>114. Time of delivery (24hr clock) <span style="border: 1px solid black; padding: 2px 5px;">H</span> <span style="border: 1px solid black; padding: 2px 5px;">H</span> : <span style="border: 1px solid black; padding: 2px 5px;">M</span> <span style="border: 1px solid black; padding: 2px 5px;">M</span><br>115. Number of babies <span style="border: 1px solid black; padding: 2px 5px;"> </span><br>If more than 1 baby, complete another Pregnancy and Delivery form, (section 9 to 12 only).<br>116. Gestational age at birth based on the best obstetric estimate <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> wks <span style="border: 1px solid black; padding: 2px 5px;"> </span> days<br>For women in the FGLS study, if the gestational age at birth is <37 weeks please contact study coordinator for the <i>Preterm Postnatal Follow-up Study</i><br>117. Fetal presentation at delivery (cross one box only)<br>Cephalic <input type="checkbox"/> Breech <input type="checkbox"/> Other <input type="checkbox"/> | 118. Apgar score at 5 minutes <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span><br>119. Newborn status at birth (cross one box only)<br>Alive <input type="checkbox"/> Intrapartum death <input type="checkbox"/><br>Antepartum death <input type="checkbox"/><br>120. Newborn sex Male <input type="checkbox"/> Female <input type="checkbox"/><br>121. Was the newborn admitted to intensive care or any special care unit? yes <input type="checkbox"/> no <input type="checkbox"/><br>122. Total amount of days spent in intensive care or special care unit (if less than 24hrs please enter 1 day) <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> days |
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**Was the newborn diagnosed with or treated for any of the following conditions before hospital discharge?**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| 123. Respiratory distress syndrome <input type="checkbox"/> yes <input type="checkbox"/> no<br>124. Transient tachypnea of the newborn <input type="checkbox"/> yes <input type="checkbox"/> no<br>125. Apnea of prematurity <input type="checkbox"/> yes <input type="checkbox"/> no<br>126. No oral feeds for more than 24hrs <input type="checkbox"/> yes <input type="checkbox"/> no<br>127. Bronchopulmonary dysplasia <input type="checkbox"/> yes <input type="checkbox"/> no<br>128. Retinopathy of prematurity <input type="checkbox"/> yes <input type="checkbox"/> no<br>129. Meconium aspiration with respiratory distress <input type="checkbox"/> yes <input type="checkbox"/> no<br>130. Hypoxic-ischaemic encephalopathy <input type="checkbox"/> yes <input type="checkbox"/> no<br>131. Hyperbilirubinaemia <input type="checkbox"/> yes <input type="checkbox"/> no<br>132. TORCH or any other intrauterine infections <input type="checkbox"/> yes <input type="checkbox"/> no<br>133. Neonatal sepsis <input type="checkbox"/> yes <input type="checkbox"/> no | 134. Necrotising enterocolitis, stage 2 or greater <input type="checkbox"/> yes <input type="checkbox"/> no<br>135. Seizures <input type="checkbox"/> yes <input type="checkbox"/> no<br>136. Hypoglycaemia <input type="checkbox"/> yes <input type="checkbox"/> no<br>137. Intraventricular haemorrhage grade 2 or greater/ periventricular haemorrhage/leukomalacia <input type="checkbox"/> yes <input type="checkbox"/> no<br>138. Hypotension requiring inotropic treatment or steroids <input type="checkbox"/> yes <input type="checkbox"/> no<br>139. Anaemia (requiring transfusion) <input type="checkbox"/> yes <input type="checkbox"/> no<br>140. Patent ductus arteriosus (requiring pharmacological treatment or surgery) <input type="checkbox"/> yes <input type="checkbox"/> no<br>141. Polycythaemia <input type="checkbox"/> yes <input type="checkbox"/> no<br>142. Any other serious condition <input type="checkbox"/> yes <input type="checkbox"/> no<br>143. Congenital abnormality (complete a neonatal abnormality form) <input type="checkbox"/> yes <input type="checkbox"/> no |
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**Section 10: Newborn anthropometry (please carry out as soon as possible, no later than 24 hours after birth)**

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| 144. Date of measurement <span style="border: 1px solid black; padding: 2px 5px;">D</span> <span style="border: 1px solid black; padding: 2px 5px;">D</span> - <span style="border: 1px solid black; padding: 2px 5px;">M</span> <span style="border: 1px solid black; padding: 2px 5px;">M</span> - <span style="border: 1px solid black; padding: 2px 5px;">Y</span> <span style="border: 1px solid black; padding: 2px 5px;">Y</span> | 145. Time of measurement (24 hr clock) <span style="border: 1px solid black; padding: 2px 5px;">H</span> <span style="border: 1px solid black; padding: 2px 5px;">H</span> : <span style="border: 1px solid black; padding: 2px 5px;">M</span> <span style="border: 1px solid black; padding: 2px 5px;">M</span> |
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| <b>1<sup>st</sup> set of anthropometric measurements</b><br>146. Weight <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> kgs<br>147. Length <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm<br>148. Head circumference <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm | <b>Repeat measurements, if required</b><br><span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> kgs<br><span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm<br><span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm | <b>Repeat measurements, if required</b><br><span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> kgs<br><span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm<br><span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm |
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| <b>INTERGROWTH-21ST</b><br><br><b>UNIVERSITY OF OXFORD</b> | <b>NEWBORN CROSS SECTIONAL STUDY</b><br><b>FETAL GROWTH LONGITUDINAL STUDY</b><br><b>Pregnancy and Delivery</b> | <b>DEV</b><br>Page 5 of 5 |
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| Study Subject Number <span style="border: 1px solid black; padding: 2px 5px;">0</span> <span style="border: 1px solid black; padding: 2px 5px;">7</span> — <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> | Study Hospital Code <span style="border: 1px solid black; padding: 2px 5px;">0</span> <span style="border: 1px solid black; padding: 2px 5px;">7</span> — <span style="border: 1px solid black; padding: 2px 5px;">1</span> |
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**Section 10: Newborn anthropometry (continued)**

| 2 <sup>nd</sup> set of anthropometric measurements                                                                                                                                                                                                                                                                                                          | Repeat measurements, if required                                                                                                                                                                                                                                                                                                                | Repeat measurements, if required                                                                                                                                                                                                                                                                                                                |
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| 149. Weight <span style="border: 1px solid black; padding: 2px 5px;"> </span> . <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> kgs | <span style="border: 1px solid black; padding: 2px 5px;"> </span> . <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> kgs | <span style="border: 1px solid black; padding: 2px 5px;"> </span> . <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> kgs |
| 150. Length <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> . <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm                                                                                                                                      | <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> . <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm                                                                                                                                      | <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> . <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm                                                                                                                                      |
| 151. Head circumference <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> . <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm                                                                                                                          | <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> . <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm                                                                                                                                      | <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> . <span style="border: 1px solid black; padding: 2px 5px;"> </span> cm                                                                                                                                      |

**Section 11: Newborn outcomes**

|                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| 152. Newborn status at hospital discharge<br>Alive <input type="checkbox"/> Alive but referred to a higher level of care <input type="checkbox"/> Dead <input type="checkbox"/> | 153. Date of hospital neonatal hospital discharge or date of death<br><span style="border: 1px solid black; padding: 2px 5px;">D</span> <span style="border: 1px solid black; padding: 2px 5px;">D</span> — <span style="border: 1px solid black; padding: 2px 5px;">M</span> <span style="border: 1px solid black; padding: 2px 5px;">M</span> — <span style="border: 1px solid black; padding: 2px 5px;">Y</span> <span style="border: 1px solid black; padding: 2px 5px;">Y</span> |
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**Section 12: Nutritional practices**

154. What was the main mode of feeding in the 24hrs prior to hospital discharge? (cross one box only)
 

|                                                |                                                                                                                                                 |                                                                                                                                             |                                            |
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| Exclusive breast milk <input type="checkbox"/> | <div style="border: 1px solid black; padding: 5px; display: inline-block;">             Predominant breast milk <input type="checkbox"/> </div> | <div style="border: 1px solid black; padding: 5px; display: inline-block;">             Partial breast milk <input type="checkbox"/> </div> | Exclusive formula <input type="checkbox"/> |
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**Section 13: Maternal outcomes**

|                                                                                         |                                                                                                                                          |
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| 155. Was the mother admitted to intensive care or any special care unit after delivery? | yes <input type="checkbox"/> no <input type="checkbox"/>                                                                                 |
| 156. If yes total number of days (if less than 24 hours, please enter as 1 day)         | <span style="border: 1px solid black; padding: 2px 5px;"> </span> <span style="border: 1px solid black; padding: 2px 5px;"> </span> days |
| 157. Maternal status at hospital discharge                                              | Alive <input type="checkbox"/> Alive but referred to a higher level of care <input type="checkbox"/> Dead <input type="checkbox"/>       |

|                                         |                                                                   |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------|-------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Name of Researcher                      |                                                                   |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Signature                               |                                                                   |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Researcher Code                         | <span style="border: 1px solid black; padding: 2px 5px;"> </span> | Date of interview                       | <span style="border: 1px solid black; padding: 2px 5px;">D</span> <span style="border: 1px solid black; padding: 2px 5px;">D</span> — <span style="border: 1px solid black; padding: 2px 5px;">M</span> <span style="border: 1px solid black; padding: 2px 5px;">M</span> — <span style="border: 1px solid black; padding: 2px 5px;">Y</span> <span style="border: 1px solid black; padding: 2px 5px;">Y</span> |
| Code of 1 <sup>st</sup> anthropometrist | <span style="border: 1px solid black; padding: 2px 5px;"> </span> | Code of 2 <sup>nd</sup> anthropometrist | <span style="border: 1px solid black; padding: 2px 5px;"> </span>                                                                                                                                                                                                                                                                                                                                               |