Early Psychosocial Development of Small for Gestational Age and Intrauterine Growth-Restricted Children: a Systematic Review

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Abbreviations: AGA: appropriate for gestational age; BW: birthweight; EFW: estimated fetal weight; FT: full-term; GA: gestational age; IUGR: intrauterine growth restriction; MCA: middle cerebral artery; PI: pulsatility index; PT: preterm; SGA: small for gestational age; UA: umbilical artery

Key words: intrauterine growth restriction, small for gestational age, early childhood, developmental outcomes, psychosocial development, behavior

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ABSTRACT

Objective: To examine evidence regarding psychosocial development from one month to four years of age in small for gestational age and intrauterine growth-restricted children.

Study Design: Studies were included if participants met criteria for small for gestational age or intrauterine growth restriction, follow-up was from age one month to 4 years, methods were described, and appropriate comparison groups were included. Methodological quality of included studies was assessed using quality-appraisal guidelines.

Results: Of 3216 studies reviewed, 24 were included. Poorer psychosocial development was described for small for gestational age children in 15 and for intrauterine growth-restricted children in 3 studies. Only 5 studies measured placental insufficiency using Doppler ultrasound. Study heterogeneity limited synthesis and interpretation.

Conclusions: Although evidence suggests that small for gestational age children are at risk of poorer early childhood psychosocial outcomes, further research is required to clarify whether placental insufficiency is associated with poorer early psychosocial development.

Key Words: small for gestational age; intrauterine growth restriction; psychosocial development; placental insufficiency; outcomes; early childhood

INTRODUCTION

Intrauterine growth restriction (IUGR) is defined by abdominal circumference or estimated fetal weight below the 3rd or 10th percentile for gestational age and placental insufficiency during fetal development.(1) IUGR is a major public health problem estimated to occur in 5-7% of pregnancies, and is associated with a higher risk of preterm birth, stillbirth, perinatal morbidity, cerebral palsy, cardiovascular disease, obesity, stroke, and diabetes.(2, 3) There is growing recognition that these infants are at increased risk of adverse perinatal outcomes relative to small for gestational age (SGA) infants, who have fetal weight below the 10th centile for gestational age but no placental insufficiency.(1) Small for gestational age infants are often constitutionally small but healthy and at lower risk of adverse perinatal outcomes.(1) Therefore, failing to differentiate between growth-restricted and small for gestational age fetuses can result in an under-identification of particularly at-risk pregnancies and over-identification of small but low-risk fetuses.(4)

Intrauterine growth-restricted infants are most commonly differentiated from small for gestational age infants using Doppler ultrasound to measure blood flow in the umbilical arteries (UA). The umbilical arteries are a pair of arteries in the umbilical cord that transport deoxygenated blood from the fetus to the placenta. Increased resistance to blood flow in these vessels, indicated by an abnormally high umbilical artery pulsatility index (PI), is a sign of placental insufficiency.(1) In particularly severe cases of placental insufficiency, blood flow in the umbilical arteries during fetal cardiac diastole can stop or reverse (i.e., absent or reversed end-diastolic flow), resulting in severe fetal distress and often necessitating premature delivery.

The fetal middle cerebral artery (MCA) may also be used to detect intrauterine growth restriction. The middle cerebral artery originates in the internal carotid artery and branches to supply blood to the lateral cerebral cortex, the anterior temporal lobes, and the insular cortices. Reduced resistance to blood flow in the fetal middle cerebral artery, indicated by an abnormally low pulsatility index, indicates redistribution of fetal circulation to the brain. This phenomenon, commonly called ‘brain-sparing,’ is an indication of fetal distress, hypoxia, and anemia. ‘Brain-sparing’ has conventionally been considered an adaptive reaction to chronic hypoxia or nutritional deprivation that maximizes blood supply to the fetal brain over less critical organs in order to prevent any further injury.(5) However, abnormal blood flow in the middle cerebral artery has been associated with poorer perinatal outcomes(6) and neonatal neurobehavior.(7) It is therefore unclear to what extent this apparently physiologically protective mechanism is detrimental to longer-term outcomes.

Recent evidence suggests that the cerebroplacental ratio may be a better method of differentiating between small for gestational age and intrauterine growth-restricted fetuses. The cerebroplacental ratio is the ratio of the PI of the middle cerebral artery to the PI of the umbilical arteries, and has been demonstrated to be a more sensitive predictor of adverse perinatal outcomes in intrauterine growth-restricted pregnancies than measuring resistance to blood flow in either the umbilical artery or middle cerebral artery alone.(2) This ratio is another index of fetal ‘brain-sparing.’ An abnormally low cerebroplacental ratio has been associated with perinatal mortality, stillbirth, and poorer early childhood development,(8) but longer-term follow-up of children with abnormal cerebroplacental ratios during fetal development is required.

Small for gestational age and intrauterine growth-restricted children are at risk of neurodevelopmental difficulties, including poorer cognitive, language, and motor outcomes.⁽⁹⁾ However, less is known about their early psychosocial development. Moreover, although evidence suggests that intrauterine growth-restricted children are at greater risk of such difficulties than small for gestational age children, most studies fail to use Doppler ultrasound to differentiate between these infants. This conflation may be due in part to the ongoing controversy regarding the most appropriate Doppler-based definition of intrauterine growth restriction,⁽⁴⁾ but limits elucidation of the specific early childhood developmental effects of placental insufficiency. Furthermore, because small for gestational age and intrauterine growth-restricted infants are often born preterm, it can be difficult to disentangle the specific impacts of reduced fetal growth or placental insufficiency on developmental outcomes. This systematic review was therefore conducted to evaluate the extent to which small for gestational age and intrauterine growth restriction were differentially associated with psychosocial developmental difficulties from age one month to four years, and to assess the quality of the available evidence.

METHODS

Search Strategy

A comprehensive literature search to identify studies was conducted using the PubMed, Embase, PsycINFO, and CINAHL databases from database inception to July 2018. Bibliographies of retrieved articles were reviewed for studies not returned by the database searches. An example electronic search strategy is provided in Supplemental Material 2.

Definitions of Study Groups

For the purposes of this review, small for gestational age was defined by estimated fetal and/or birth weight $< 10^{\text{th}}$ percentile for gestational age. Both 1) studies that used this weight cut-off without reference to Doppler ultrasound parameters, and 2) studies that explicitly excluded children with abnormal blood flow during fetal development as measured by Doppler ultrasound were considered to involve small for gestational age children. The first type of study may include intrauterine growth-restricted children in their study groups and therefore conflates small for gestational age and intrauterine growth restriction due to a failure to include Doppler ultrasound data in the study design. The second type explicitly exclude intrauterine growth-restricted children and therefore assess only small for gestational age children.

In contrast, intrauterine growth restriction was defined by estimated fetal and/or birth weight $< 10^{\text{th}}$ percentile for gestational age *and* abnormal blood flow in the umbilical arteries and/or middle cerebral artery and/or an abnormal cerebroplacental ratio. Studies that included term and/or preterm small for gestational age and/or intrauterine growth-restricted children were included in this review to increase inclusivity.

Selection of Eligible Studies

A PRISMA flow chart of the study exclusion process is shown in Figure 1. The initial database search returned 3216 studies. After a review of titles, 2544 articles were

excluded. Abstracts of the remaining 672 studies were then reviewed, and a further 33 studies were excluded. Full-text analysis of 639 studies was then conducted; studies were determined to be ineligible if study participants did not meet specified criteria for small for gestational age (estimated fetal or birth weight < 10th percentile for gestational age) or intrauterine growth restriction (estimated fetal or birth weight < 10th percentile for gestational age and an umbilical artery pulsatility index > 95th percentile) (n=313), follow-up was not from one month to ≤48 months of age (n=209), study methods were not adequately described (n=0), children with congenital anomalies were not explicitly excluded (n=17), (4) appropriate for gestational age (estimated fetal weight between 10th-90th centile for gestational age) comparison group(s) were not included (n=1), psychosocial data were not presented separately (e.g., social behavior and language development conflated) (n=51), or full English version was not available (n=16).

Although excluding studies due to language of publication introduces bias, it was not possible to have studies translated into English for the purposes of this review. Excluding studies conducted in the neonatal period (n=8) excludes most studies that only collect neurobehavioral data. Neurobehavioral data were defined as measures relating solely to neurological status as assessed by the observation of behavior, i.e., gaze or state change. Only studies published in peer-reviewed journals were included in this review; dissertations, conference proceedings, abstracts, and book chapters were excluded. A total of 615 studies did not meet the inclusion criteria following full-text analysis, and 24 were eligible for inclusion in this review.

Data Extraction and Synthesis

Data were retrieved using a specifically designed data-extraction form that included authors, year of publication, location of study, age at assessment, study and comparison group(s), measures used, exclusion criteria, covariates, and summary results. The studies eligible for inclusion in this review varied widely with respect to study and control group definitions, ages at assessment, and assessment measures used. This heterogeneity in study design prevented quantitative synthesis of the evidence in the form of a meta-analysis. A descriptive methodology was therefore chosen, and the results are presented as a narrative synthesis of the literature related to psychosocial developmental outcomes of both term and preterm small for gestational age and intrauterine growth-restricted children.

Quality Assessment

A suitable tool for assessing the quality of evidence relating to prognostics and health outcomes was used.⁽¹⁰⁾ This tool evaluates six areas of potential bias: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding factor analysis, and data analysis.

RESULTS

Included Studies

A total of 24 studies that assessed the early psychosocial development of small for gestational age or intrauterine growth-restricted children were identified and are summarized Table 1 and detailed in Supplemental Material 1. In 15 of the 24 included studies, psychosocial outcomes in intrauterine growth restriction or small for gestational

age children were poorer than those with normal intrauterine growth. The included studies were all prospective and were conducted in Spain (8), the United States (4), New Zealand (3), Australia (2), Canada (2), the United Kingdom (2), Israel (1), the Netherlands (1), and Brazil (1).

One Month to One Year

Eight studies were conducted from age one month to one year. None used Doppler ultrasound to assess placental insufficiency. One study found that the homes of small for gestational age infants were less stimulating and supportive of infant learning and development than those of appropriate for gestational age infants, that maternal perceptions of small for gestational age infants' negative reactivity were related to lower home environment quality and less warm and responsive parenting, and that perceived difficult temperament at 3 months in small but not appropriate for gestational age infants matched for gender and parity was associated with subsequent lower-quality parental behavior.(11)

Using the Behavior Assessment of Infant Temperament, Halpern et al. found that at 8 months, small for gestational age infants only differed significantly from appropriate for gestational age infants on attention, and that small for gestational age infants' attention did not improve until 12 months.(12) Another study by this group demonstrated that small for gestational age infants had poorer attention than appropriate for gestational age peers, and that mothers of small for gestational age infants engaged in significantly less reciprocal play than mothers of appropriate for gestational age infants.(13)

Using the Bayley Scales of Infant Development, second edition Behavior Rating Scale, small for gestational age infants scored significantly worse than appropriate for gestational age peers at 2 but not 6 or 12 months. At 2 months, small for gestational age children scored significantly more poorly on positive affect, soothability when upset, energy, exploration of objects and/or surroundings, and orientation to the examiner than appropriate for gestational age peers.(14) Using the Griffiths Mental Development Scales and the Short Infant Temperament Scale for Infants at four months corrected, small for gestational age infants scored significantly lower on cooperation than appropriate for gestational age infants matched for gestational age, race, and sex.(15)

Robson & Cline, using the Carey Infant Questionnaire at 7 months, found no significant differences between small and appropriate for gestational age infants.(16) Watt found that full-term small for gestational age infants showed less approaching behavior and were more intense than preterm appropriate for gestational age infants at 6 months. Moreover, in small for gestational age mother-infant dyads, maternal vocalizations were positively correlated with difficult infant temperament.(17) At 3 months, Feldman et al. found no significant difference in negative engagement between small and appropriate for gestational age children matched for birth weight or gestational age.(18)

Therefore, in 6 of the 8 studies conducted from one month to one year of age, small for gestational age infants had significantly poorer psychosocial development than appropriate for gestational age infants. However, there appear to be no studies on the psychosocial development of intrauterine growth-restricted infants in this age range.

One to Two Years

SGA. Eight studies measured psychosocial development from 1 to 2 years of age. Five of these studies relied on a fetal or birth weight definition without reference to Doppler parameters. Using the Parental Bonding Instrument, the Infant and Toddler Social Emotional Assessment, and the Early Childhood Behavior Questionnaire, small for gestational age children whose mothers reported lower self-perceived maternal care during their own infancies scored lower on both attentional set shifting and attention at 18 months.(19)

Watt measured infant temperament at 20 months and found that full-term small for gestational age infants were more active than preterm appropriate for gestational age infants and had lower thresholds than both preterm and full-term appropriate for gestational age infants. This study also reported that temperament dimensions at 6 and 20 months were not correlated.(17) Batalle et al.(20) and Simoes et al.(21) found that small for gestational age children did not score significantly differently from appropriate for gestational age children on the social-emotional or adaptive behavior subscales of the Bayley Scales of Infant and Toddler Development, third edition. Likewise, differentiating between small for gestational age and ‘intrauterine growth-restricted’ children according to whether fetal abdominal circumference changed by less than (‘small for gestational age’) or more than (‘intrauterine growth-restricted’) -1.5 SDs between the first and last scan, Roth et al. found no differences among adaptive or personal-social behavior in small for gestational age, ‘intrauterine growth-restricted,’ and appropriate for gestational age children.(22) It should be noted that these are not currently accepted definitions of either small for gestational age or intrauterine growth restriction.

IUGR. Three studies conducted with children from 1 to 2 years of age used Doppler parameters to differentiate between small for gestational age and intrauterine growth-restricted children. Esteban et al.(23) and Padilla et al.(24) defined intrauterine growth restriction as estimated fetal weight <10th centile for gestational age and abnormal umbilical artery pulsatility index, and found that preterm intrauterine growth-restricted children scored significantly more poorly than full-term appropriate for gestational age children on the adaptive behavior but not the social-emotional subscale of the Bayley Scales of Infant and Toddler Development, third edition. However, preterm intrauterine growth-restricted children did not score significantly differently on these two subscales compared to preterm appropriate for gestational age children matched for gestational age.

Using the Behavior Rating Scale to measure emotional lability and task orientation in 219 small for gestational age children, smaller head circumference and cord blood acidosis, which may indicate fetal asphyxia, were associated with lower Behavior Rating Scale scores.(25) However, abnormal umbilical artery Doppler parameters, birth weight z-scores, and gestational age were not associated with Behavior Rating Scale scores. Therefore, of the 8 studies conducted with children between 1 and 2 years of age, 5 found significant psychosocial differences between small for gestational age or intrauterine growth-restricted and appropriate for gestational age children.

Two to Three Years

SGA. Eight studies examined psychosocial development between 2 and 3 years of age. Only 2 studies used Doppler ultrasound to differentiate between small for gestational age and intrauterine growth-restricted children. Figueras et al. only included small for

gestational age children with normal umbilical artery Doppler, thereby explicitly excluding intrauterine growth-restricted children. These small for gestational age children scored significantly worse on the personal-social subscale of the Ages and Stages Questionnaire than appropriate for gestational age children matched for gestational age, socioeconomic status, and parity.(26) Similarly, in another study, term small for gestational age children with normal umbilical artery Doppler scored significantly lower than term appropriate for gestational age children matched for gestational age in the social-emotional and adaptive behavior domains of the Bayley Scales of Infant and Toddler Development, third edition.(27)

Very preterm children who screened positive for autism using the Modified Checklist for Autism in Toddlers (M-CHAT) at age 2 had a significantly greater incidence of small for gestational age.(28) Very preterm small for gestational age children had higher anxious/depressed, withdrawn, internalizing, and total problem scores on the Child Behaviour Checklist after adjustment for both medical and social confounders than very preterm appropriate for gestational age children.(29) Confounders in these analyses included antenatal glucocorticosteroid use, gestational age, gender, birthweight, extra-uterine transport, hypotension, bronchopulmonary dysplasia, postnatal dexamethasone, periventricular leukomalacia, intraventricular hemorrhage, socioeconomic status, ethnicity, and maternal age.

Feldman et al. assessed at age 2 years small for gestational age children, appropriate for gestational age children matched for birth weight, and appropriate for gestational age children matched for gestational age, and found that small and appropriate for gestational age children matched for birthweight demonstrated significantly more

negative engagement than appropriate for gestational age children matched for gestational age.(18) In contrast, Johnson et al. found no differences in social competence in late and moderately preterm small for gestational age children, stratified by birthweight either <3rd or 3rd-10th percentile for gestational age, in comparison with late and moderately preterm appropriate for gestational age peers using the Brief Infant and Toddler Social Emotional Assessment.(30)

Eixarch et al. used the Ages and Stages Questionnaire to compare appropriate for gestational age children matched for gestational age to small for gestational age children with normal middle cerebral artery pulsatility index, and found that small for gestational age children had significantly poorer personal-social development than appropriate for gestational age children.(31)

IUGR. Two studies conducted with children from 2 to 3 years of age used Doppler parameters to differentiate between small for gestational age and intrauterine growth-restricted children.(32) Padilla et al. defined intrauterine growth restriction by fetal weight < 10th percentile confirmed at birth and an abnormal umbilical artery pulsatility index. This group found that a small cohort of preterm, growth-restricted children were approximately three times more likely to screen positive for autism using the M-CHAT compared to preterm, appropriate for gestational age children matched for gestational age. Furthermore, growth-restricted children were about five times more likely to screen positive than term, appropriate for gestational age children.

Eixarch et al. used the Ages and Stages Questionnaire to compare small for gestational age children with normal or abnormal (<5th centile) middle cerebral artery pulsatility index.(31) The difference in personal-social development between these

groups did not reach significance. The authors comment that this challenges other evidence that cerebral blood flow redistribution is a protective adaptation in small for gestational age fetuses.(31)

Thus, 7 of the 8 studies conducted between 2 and 3 years found significant psychosocial differences between small for gestational age or growth-restricted and appropriate for gestational age children. However, only two of these studies differentiated between small for gestational age and intrauterine growth-restricted children using Doppler ultrasound.

Three to Four Years

Two studies assessed psychosocial development between 3 and 4 years of age. Both of these studies used birthweight <10th centile for gestational age to define small for gestational age. Sung et al. found that preterm small for gestational age infants had lower attention than gestational age- but not birthweight-matched appropriate for gestational age infants, and a lower mood score than either comparison group, which suggests that small for gestational age is a further risk factor for psychosocial development in preterm children.(33) This study found no significant differences in total abnormal behaviors, approach, cooperation, persistence, or activity. Using the Strengths and Difficulties Questionnaire at 3.5 years, Cornforth et al. found no significant differences between small and appropriate for gestational age children.(34) Thus, one of the two studies conducted between 3 and 4 years of age found significant psychosocial differences between small and appropriate for gestational age children. However, there are currently

no studies assessing the psychosocial development of intrauterine growth-restricted children as differentiated using Doppler ultrasound of the umbilical artery.

Quality of Studies

The source population from which study participants were drawn was poorly described in 4(20, 22, 25, 31) and only partly described in 9 studies.(11-13, 17, 18, 23, 26, 28, 32) Study populations were described and representative in all included studies. Although most studies were small, 11 included more than 100 children.(15, 18, 19, 25-31, 34) Ten studies failed to provide reasons for reported loss of participants to follow-up,(11, 12, 14, 17, 19-21, 26, 28, 31) and 10 failed to report whether there were significant differences between participants included and those lost to follow-up.(12-14, 17, 20-23, 27, 30) Parents lost to follow-up were significantly younger,(25, 34) less educated,(15, 25, 34) of lower socioeconomic status,(29, 34) of an ethnic minority background,(15, 25, 29) unmarried,(34) and smokers,(34) while infants lost to follow-up were more likely to have experienced more perinatal morbidity,(26) had higher birthweight if preterm and higher gestational age if term,(28) had less bronchopulmonary dysplasia or postnatal dexamethasone,(29) and to be male.(15) All studies adequately defined and measured prognostic factors and outcomes. Adjustment for social or medical confounding factors was absent or unreported in 10 of the 24 studies.(12, 14, 17, 18, 22-24, 26, 32, 33) Statistical analysis was partly described in 2 studies(17, 33) and inadequately described in 1 study, and only 1 study(33) had inadequate data reporting.

DISCUSSION

The literature reviewed here suggests that small for gestational age children may be at increased risk of poorer early childhood psychosocial development than their appropriate for gestational age peers, while highlighting the stark lack of evidence regarding the impact of placental insufficiency on early childhood psychosocial outcomes. This systematic review identified 24 studies that assessed psychosocial outcomes in small for gestational age or intrauterine growth-restricted children. Fifteen of the 24 studies reported that small for gestational age children are at risk of poorer psychosocial functioning than their appropriate for gestational age peers, including mother-infant interaction,(11, 13, 17, 18) infant reactivity and temperament,(12-15, 17, 18, 33) attention,(12-14, 19, 33) mood,(33) personal-social(14, 15, 21, 22, 26, 27, 31) and adaptive behavior,(27) autistic symptoms,(28) and internalizing behaviors.(29)

Eight studies were conducted from 1 month to 1 year of life, 8 from 1 to 2 years of age, 8 from 2 to 3 years of age, and 2 from 3 to 4 years of age. Most of the evidence therefore relates to psychosocial development within the first 2 years of life. This may be due in part to the relative ease of recruiting study participants for short-term or cross-sectional studies compared to the expense and attrition challenges associated with longitudinal studies. Nevertheless, this imbalance makes it difficult to determine whether psychosocial outcomes observed in the first years of life are sustained throughout early childhood. This scarcity of evidence is particularly apparent in the third year of life, as only 2 studies exist in this period and neither included diagnosis of placental insufficiency using Doppler ultrasound.

Only 4 studies included a study group of intrauterine growth-restricted infants with abnormal umbilical artery pulsatility index.(23-25, 32) These studies found an

association between placental insufficiency and poorer personal-social and adaptive behavior and symptoms of autism in preterm intrauterine growth-restricted infants.(23, 24, 32) One study reported measuring blood flow in the middle cerebral artery. Eixarch et al. compared small for gestational age children with normal umbilical artery pulsatility index and either normal or abnormal middle cerebral artery pulsatility index, and found no differences between these groups of children in relation to personal-social behavior.(31) None of the included studies specifically reported the psychosocial outcomes of children following abnormal cerebroplacental ratio. There is therefore no evidence available regarding the potential effects of abnormal cerebroplacental ratio on early childhood psychosocial outcomes. Uniquely, McCowan et al. found that a base deficit in the umbilical artery was associated with poorer behavioral outcomes.(25) Further research into the impact of abnormal maternal-fetal or fetoplacental blood flow as measured by Doppler ultrasound on early childhood psychosocial development is greatly needed.

Infants born small for gestational age or following placental insufficiency are at higher risk of preterm birth, and prematurity has been thoroughly associated with a variety of adverse developmental outcomes.(35) Despite several landmark trials,(36-39) there is a lack of consensus regarding optimal delivery timing and delivery criteria for growth-restricted fetuses between 34-38 weeks' gestation.(40, 41) Although delaying the delivery of growth-restricted fetuses can improve outcomes, this may not be possible in the context of oligohydramnios, obstetric emergencies, severe preeclampsia, or other indications for delivery.(40, 41) It is therefore important to include gestational age in the design of studies about the psychosocial development of small for gestational age and

intrauterine growth-restricted children. Potential conflation of the differential effects of prematurity and reduced fetal growth or placental insufficiency on early childhood psychosocial development was addressed variously across the studies in this review. Many studies examined or included gestational age or prematurity as a covariate,(15, 16, 20, 21, 23, 24, 27, 29, 33) nine matched control children for gestational age,(15, 18, 23, 24, 26, 27, 31-33) four included only preterm(30) or full-term children,(11, 12, 14, 31) and four included distinct groups of full-term and preterm control children.(17, 23, 24, 32) The majority of the studies included in this review therefore make efforts to distinguish between the impact of gestational age and reduced fetal growth or placental insufficiency on early childhood psychosocial development. However, it is imperative that future studies carefully attend to gestational age and prematurity in relation to both study group definitions and statistical analyses.

The psychosocial difficulties experienced in early childhood reported in the studies included in this review may translate into poorer long-term outcomes. Behavioral problems in early childhood predict depression, anxiety, and internalizing and externalizing behavioral problems in adolescence and adulthood, as well as substance abuse, relationship problems, academic difficulties, and criminal activity.(42) These symptoms tend to negatively impact children and limit social engagement.(43, 44) These children may be prone to sadness, fear, shyness, shame, rumination, poor social competence, and poor attentional regulation.(43) Internalizing children are less likely to approach other children(45) and may both perceive themselves to be less socially accepted by peers(44) and actually be less socially appealing to other children.(45) They may also have difficulties learning to cope with stress, novelty, or negative emotions, and

have relatively low flexibility, spontaneity, and impulsivity.(45) Early childhood developmental assessment studies of these two high-risk populations therefore represent a valuable addition to the evidence while also providing support for evidence-based early interventions that may ameliorate some of the developmental difficulties experienced by small for gestational age or intrauterine growth-restricted children.

This systematic review has several limitations. Excluding studies not available in English introduces a language bias. The quality assessment tool does not provide numerical quality marks for each study, and it is therefore not possible to rank the quality of the included studies quantitatively. It is also possible that other researchers may have judged the quality of the included studies differently. Including only published studies in peer-reviewed journals and excluding dissertations, conference proceedings, abstracts, and book chapters can result in exclusion of relevant available data. Finally, and most importantly, inconsistent study and control group definitions, ages at assessment, and assessment measures used made it impossible to conduct an adequate meta-analysis of the evidence, which would have further facilitated synthesis and interpretation.

In summary, evidence suggests that small for gestational age children are at increased risk of early childhood psychosocial difficulties. However, much less is known about these outcomes following placental insufficiency during fetal development. Future studies would benefit from longitudinal designs with repeated developmental assessments throughout early childhood. Moreover, including groups of children born at different gestational ages with and without abnormal umbilical artery and middle cerebral artery pulsatility indices and cerebroplacental ratios would improve understanding of the psychosocial outcomes of these populations and clarify the potential impact of delivery

timing on their early psychosocial development. Increased sample sizes, more thorough and consistent adjustment for both social and medical confounding factors, comparison of included participants with those lost to follow-up, and increased recruitment of participants from socioeconomically vulnerable and regionally diverse populations would further reduce bias and improve the quality of evidence regarding the psychosocial development of small for gestational age or intrauterine growth-restricted children.

Supplementary information is available at JPER's website.

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Titles and Legends of Figures and Tables

Table 1: Summary of Findings

Table 1. Summary of Findings

	1 Month - 1 Year	1 - 2 Years	2 - 3 Years	3 - 4 Years
Small for Gestational Age	<p>Poorer outcomes in 6 studies, including attention, positive affect, soothability, cooperation, and approaching behavior</p> <p>No differences in 2 studies</p>	<p>Poorer outcomes in 2 studies, including attention and activity levels</p> <p>No differences in 3 studies</p>	<p>Poorer outcomes in 6 studies, including personal-social, social-emotional, adaptive, anxious/depressed, withdrawn, and internalizing behavior; autism; and negative engagement</p> <p>No differences in 1 study</p>	<p>Poorer attention and lower mood but no differences in abnormal behavior, approach, cooperation, persistence, or activity in 1 study</p> <p>No differences in 1 study</p>
Intrauterine Growth-Restricted	<p>No studies available</p>	<p>Poorer adaptive behavior in 2 studies</p> <p>No differences in 1 study</p>	<p>Increased risk of autism in 1 study</p>	<p>No studies available</p>