

Antenatal Depression and Infant Sleep: Investigating the pathways of risk



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ABSTRACT

Antenatal Depression and Infant Sleep: Investigating the pathways of risk

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Introduction: Maternal antenatal depression has been associated with an increased risk of offspring psychopathology and more recently with disturbed infant sleep; in particular, shorter sleep duration, more awakenings and sleep problems. The exact mechanisms through which risk may be transmitted remain unknown, as does the question of whether all infants are equally susceptible to the effects of antenatal depression. The primary objectives of this thesis were to examine:

- i) The role of two potential moderators on the association between antenatal depression and infant sleep: infant reactive temperament and the serotonin transporter polymorphism 5-HTTLPR
- ii) The association between antenatal depression and infant sleep using objective behavioural and physiological measures.
- iii) Infant sleep and temperament in a pilot randomised controlled trial (RCT) following treatment of antenatal depression

Methods

- i) The role of infant reactivity and 5-HTTLPR as potential moderators was examined in two large longitudinal cohorts: the Avon Longitudinal Study of Parents And Children (ALSPAC) and the Generation R study, based in the UK and The Netherlands respectively (n=8,991 and n=2,441).
- ii) An Oxford based pilot longitudinal family study (n=16)
- iii) A pilot randomised controlled trial of women with antenatal depression who received Cognitive Behavioural Therapy (CBT) or Care as Usual (n=25).

Results

- i) There was evidence that reactive temperament moderated the association between antenatal depression and infant sleep; boys seemed to be most affected exhibiting more awakenings, sleep problems and shorter sleep duration. 5-HTTLPR did not moderate this association.
- ii) Antenatal depression was associated with shorter infant sleep duration 5 months postpartum
- iii) Improvement in depression was associated with shorter infant sleep duration and easier temperament 2 months postpartum

Conclusion: This thesis suggests that not all infants are equally susceptible to environmental influences and this may prove important in targeting interventions. The role of genetic factors in conferring any susceptibility remains unclear. Actigraphy offering accurate representation of activity levels and timing during the day and night was a significant methodological advantage, but recruitment to a study incorporating these proved challenging. Finally, psychological interventions during pregnancy appear to have beneficial effects for child development.

STATEMENT OF CONTRIBUTION

This thesis comprised of four distinct datasets.

For Chapters 2 and 3 the ALSPAC and Generation R cohorts were used. The data for both cohorts had already been collected at the time that this thesis was undertaken. I was not involved in the data collection or selection of measures. I conceptualised the research questions, I planned the statistical analysis to address them and carried out the analysis with guidance from my supervisors Dr Paul Ramchandani and Dr Katharina Wulff and our collaborators from the Generation R project Marinus van IJzendoorn and Marian Bakermans-Krannenburg. I also constructed the necessary variables where these were not available.

Chapter 4 involved primary data collection. I was solely responsible for the design of this study, obtaining ethical approval and all necessary R&D approvals from the Oxford University Hospitals NHS Trust. I undertook all the data collection, prepared the analysis plan and carried out the analysis of data.

Chapter 5 used data from the Anticipate trial. This was a pilot RCT trial which took place in Bristol, UK. I was partly involved in the design stage by choosing the assessment measures for infant outcomes with the guidance of Dr Ramchandani who was also involved in other parts of the design. I designed the research questions and analysis plan, constructed the necessary variables and carried out the analysis.

This thesis is composed of my original work. I have stated the contribution of others to my thesis where this is appropriate, including statistical planning and data analysis.

CONTENTS

Acknowledgments	ii
Abstract.....	iii
Statement of Contribution	iv
List of Tables	xii
List of Figures.....	xvi
List of Abbreviations	xviii
Chapter 1 Introduction.....	20
1.1 <i>Antenatal depression</i>	21
1.1.1 Antenatal depression & child development	22
1.1.2 Fetal Programming & The developmental origins of health and disease	
23	
1.1.3 Mechanisms through which antenatal depression affects child	
development.....	24
1.2 <i>Infant Sleep</i>	28
1.2.1 Brief Introduction to Sleep.....	28
1.2.1.1 The Two Process Model.....	28
1.2.1.2 The Stages of Sleep	29
1.2.2 Sleep development in children	29
1.2.2.1 In utero	30
1.2.2.2 From birth to 12 months of life	30
1.2.2.3 1 -5 years of age	33
1.2.3 Why is sleep an important aspect of child development.....	34
1.2.3.1 Sleep, Cognition and Language	35
1.2.3.2 Sleep and Emotional and Behavioural Problems	36
1.2.4 The aetiology of sleep-wake behaviour	38
1.2.4.1 Heritability/Genes	38
1.2.4.2 GxE interactions.....	40
1.2.4.3 Environmental influences.....	41
1.2.5 Measurement of sleep	45
1.2.5.1 Sleep questionnaires and diaries	45
1.2.5.2 Polysomnography.....	46

1.2.5.3	Actigraphy.....	46
1.3	<i>Antenatal depression and infant sleep</i>	49
1.3.1	Animal research on antenatal stress and offspring sleep.....	49
1.3.2	Research on antenatal depression and infant sleep in humans	49
1.3.3	Summary of findings.....	54
1.4	<i>Rationale & research strategy</i>	58
1.5	<i>Aims and Structure of the thesis</i>	59
 Chapter 2: Antenatal depression and infant sleep: The moderating effects of infant reactivity: An investigation in the ALSPAC and Generation R cohorts ... 60		
2	Chapter Overview	61
2.1	<i>Introduction</i>	62
2.1.1	Diathesis-Stress Model	62
2.1.2	The theory of differential susceptibility (DST).....	63
2.1.2.1	Criteria For Establishing Differential Susceptibility	64
2.1.3	Reactive temperament as a susceptibility factor	65
2.1.4	Antenatal depression and infant temperament	69
2.1.5	Infant sleep and reactive temperament.....	71
2.1.6	Rationale	74
2.1.7	Aims & Hypotheses	74
2.2	<i>STUDY I - The Avon Longitudinal Study of Parents and Children (ALSPAC)</i> 75	
2.2.1	Methods.....	75
2.2.1.1	Setting and Procedure	75
2.2.1.2	Participants.....	75
2.2.1.3	Measures	79
2.2.1.4	Analysis Plan	81
2.2.2	Results.....	84
2.2.2.1	Treating the Data.....	84
2.2.2.2	Descriptive Statistics.....	84
2.2.2.3	Correlational analyses of sleep variables	87
2.2.2.4	Moderator analysis	90
2.2.2.5	Sleep at 30 months of age: Does reactivity moderate the association between antenatal depression and infant sleep at 30 months of age (total sleep time, awakenings and sleep problems)?.....	96

2.3	<i>Study II – Generation R</i>	99
2.3.1	Methods.....	99
2.3.1.1	Setting and Procedure	99
2.3.1.2	Participants.....	99
2.3.1.3	Measures	104
2.3.1.4	Analysis Plan	105
2.3.2	Results.....	107
2.3.2.1	Treating the Data.....	107
2.3.2.2	Descriptive Statistics.....	107
2.3.2.3	Differences in Sleep, Depression and Reactivity by Ethnic Background ..	109
2.3.2.4	Correlational Analyses	109
2.3.2.5	Moderator analysis	111
2.4	<i>Discussion</i>	115
2.4.1	Setting the findings in context	116
2.4.1.1	Criteria for Differential Susceptibility	117
2.4.2	Strengths and Limitations	117
2.4.3	Conclusion	119
Chapter 3: Antenatal depression and infant sleep; examining the potential moderating effect of the serotonin transporter promoter polymorphism		120
3	Chapter Overview	121
3.1	<i>Introduction</i>	122
3.1.1	The serotonergic system.....	122
3.1.1.1	Synthesis of Serotonin	123
3.1.2	The serotonin transporter (5-HTT).....	123
3.1.3	Genetics of the serotonin transporter (SLC6A4)	123
3.1.4	Serotonin and sleep	124
3.1.5	Gene x Environment Interaction	125
3.1.5.1	Interaction of early life stress and 5-HTTLPR.....	125
3.1.5.2	Methodological Issues in GxE research	126
3.1.5.3	Genetic Variation of 5-HTTLPR and sleep.....	128
3.1.5.4	Summary of studies.....	131
3.1.6	Antenatal depression and 5-HTTLPR.....	132
3.1.7	The Bright Side - The Theory of differential susceptibility in GxE research	133

3.1.8	Rationale	134
3.1.9	Aims and Hypotheses.....	135
3.2	<i>STUDY I - The Avon Longitudinal Study of Parents And Children (ALSPAC)</i>	
	136	
3.2.1	Methods.....	136
3.2.1.1	Setting and Procedure	136
3.2.1.2	Participants.....	138
3.2.1.3	Measures	140
3.2.1.4	Analysis Plan	141
3.2.2	Results.....	142
3.2.2.1	Treating Data.....	142
3.2.2.2	Descriptive Statistics.....	142
3.2.2.3	Correlational analyses of sleep variables	147
3.2.2.4	Moderator analysis	149
3.3	<i>Study II - Generation R</i>	154
3.3.1	Methods.....	154
3.3.1.1	Participants.....	154
3.3.1.2	Measures	157
3.3.1.3	Analysis Plan	157
3.3.2	Results.....	159
3.3.2.1	Treating the Data.....	159
3.3.2.2	Descriptive statistics	159
3.3.2.3	Correlational analyses	162
3.3.2.4	Moderator analysis.....	163
3.4	<i>Discussion</i>	167
3.4.1	The findings into context	168
3.4.2	Strengths and Limitations	169
3.4.3	Conclusion	171
Chapter 4: An investigation of the association between antenatal maternal depression and infant sleep, using detailed observational measures.....		172
4 Chapter Overview		173
4.1	<i>Introduction</i>	174
4.1.1	Mechanisms	174
4.1.1.1	Maternal cognitions.....	174
4.1.1.2	Temperament	175

4.1.1.3	Maternal and Infant Cortisol	175
4.1.1.4	Maternal sleep	177
4.1.2	Aims	179
4.2	<i>Methods</i>	180
4.2.1	Design	180
4.2.2	Procedure	180
4.2.2.1	Recruitment.....	180
4.2.2.2	Antenatal Home Visit.....	181
4.2.2.3	Postnatal Home Visit	181
4.2.3	Participants.....	182
4.2.4	Measures:	184
4.2.4.1	Mental Health.....	184
4.2.4.2	Parental and infant Sleep.....	185
4.2.4.3	Infant temperament	189
4.2.4.4	Cortisol.....	190
4.2.4.5	Socio—demographic information	190
4.2.5	Statistical Analysis Plan.....	192
4.3	<i>Results</i>	193
4.3.1	Feasibility of the Study	193
4.3.1.1	Recruitment.....	193
4.3.1.2	Antenatal Phase.....	194
4.3.1.3	Postnatal Phase.....	194
4.3.1.4	Partners’ Participation.....	195
4.3.2	Analysis of Primary outcomes	196
4.3.2.1	Descriptives.....	196
4.3.2.2	Associations between Maternal Depressive Symptoms and infant sleep as measured by actigraphy and questionnaire	197
4.3.2.3	Associations between infant actigraphy and maternal report of infant sleep 202	205
4.3.3	Analysis of Secondary outcomes	205
4.3.3.1	Associations between Maternal Cognitions about Sleep and Infant Sleep.	205
4.3.3.2	Associations between Maternal Depressive Symptoms and Temperament	207
4.3.3.3	Maternal and Infant Cortisol	209
4.3.3.4	Maternal Sleep ante- and postnatally	211
4.4	<i>Discussion</i>	218
4.4.1	The findings	218

4.4.2	Strengths and Limitations	221
4.4.3	Future research.....	222
Chapter 5: A pilot randomized controlled trial of cognitive behavioural therapy for women with antenatal depression; infant outcomes		223
5	Chapter Overview	224
5.1	<i>Introduction</i>	225
5.1.1	Aims	230
5.2	<i>Methods</i>	231
5.2.1	Design	231
5.2.2	Sample.....	231
5.2.3	Measures	234
5.2.3.1	Depression.....	234
5.2.3.2	Infant Temperament	235
5.2.3.3	Infant Sleep	235
5.2.4	Procedure	235
5.2.4.1	The trial	235
5.2.4.2	Recruitment.....	235
5.2.4.3	Baseline Assessment – Time 1.....	236
5.2.4.4	Cognitive Behavioural Therapy (CBT).....	237
5.2.4.5	Care as Usual	237
5.2.4.6	Post Treatment Assessment – Time 2	237
5.2.4.7	Postnatal Assessment – Time 3.....	237
5.2.5	Statistical Analysis.....	239
5.3	<i>Results</i>	240
5.3.1	Primary Outcome of RCT	240
5.3.2	Descriptive Statistics.....	240
5.3.3	Aim 1: Analysis by treatment arm	240
5.3.4	Aim 2: Associations between change in depressive symptoms, infant sleep and temperament.....	242
5.3.5	Associations of Infant Sleep and Difficult Temperament with Postnatal depression	246
5.3.5.1	Controlling for Postnatal Depression	246
5.3.5.2	Controlling for Infant Temperament	247
5.3.6	Subsequent Analysis	247

5.3.6.1	Associations between change in Depression Scores, Depression at Baseline and SSRI use	247
5.3.6.2	Associations between maternal SSRI use and infant outcomes	247
5.3.6.3	Associations between breastfeeding and infant sleep	247
5.4	<i>Discussion</i>	249
5.4.1	The findings	249
5.4.2	Understanding the findings	250
5.4.3	Potential Explanations.....	250
5.4.3.1	Post Hoc Explanations	251
5.4.4	Strengths and Limitations	253
6	Discussion.....	256
6.1	<i>The Findings</i>	257
6.2	<i>The concept of Optimal Sleep</i>	262
6.3	<i>Different Methodological Approaches</i>	262
6.4	<i>Overall Strengths and Limitations of the thesis</i>	266
6.4.1	Strengths	266
6.4.2	Limitations	266
6.5	<i>Implications</i>	268
6.5.1	For Future Research	268
6.5.2	For Public Health	268
6.5.3	Further Investigation	269
6.5.4	Conclusion	270
List of Appendices		272
<i>Appendices for Chapter 2</i>		275
<i>Appendices for Chapter 3</i>		292
<i>Appendices for Chapter 4</i>		310
<i>Appendices for Chapter 5</i>		329
References		332

LIST OF TABLES

Table 1: Studies which have examined the association between antenatal maternal depression and child sleep.	56
Table 2: Characteristics of studies reporting differential susceptibility using temperament as a susceptibility factor.	68
Table 3: Comparison of demographic characteristics of the current sample (n=8,991) and the whole ALSPAC sample (n=14,062).....	78
Table 4: Descriptives for antenatal depression at 32 weeks gestation and reactivity 6 months postpartum (n=9,868).....	84
Table 5: Descriptives for total sleep time, awakenings and sleep problems in the ALSPAC cohort.....	86
Table 6: Unadjusted associations for sleep variables at 6, 18 and 30 months of age (n=8,052)	88
Table 7: Unadjusted associations between sleep variables, reactivity, depression scores and covariates at 6, 18 and 30 months of age (n=8,007).....	89
Table 8: Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and total sleep time at 6 months (n=8,678).....	91
Table 9: Summary of Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on the association between antenatal depression and number of awakenings at 6 months, Step 4 (n=8,909).....	92
Table 10 : Summary of Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and a) sleep duration, b) number of night awakenings and c) sleep problems at 18 months, Step 4.	94
Table 11: Summary of Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and a) sleep duration, b) number of night awakenings and c) sleep problems at 30 months, Step 4.	97
Table 12: Overview of the ALSPAC and Generation R cohorts and description of key variables	101
Table 13: Comparison of demographic characteristics of the current sample (n=2,241) and the whole Generation R sample (n=7,795).	102
Table 14: Descriptives for antenatal depression at 32 weeks and reactivity 6 months postpartum (n=2,383).	107
Table 15: Descriptives for sleep data at 6 and 24 months of age.	108
Table 16: Comparison of Dutch/European vs. non-European participants in Generation R study	109
Table 17: Unadjusted bivariate associations of sleep variables at 6 and 24 months	110

Table 18: Unadjusted associations between sleep variables at 6 and 24 months and reactivity, depression scores and covariates.	110
Table 19: Summary of Hierarchical Regression Model testing the moderating effect of reactivity and gender on the association between antenatal depression and infant sleep at 6 months of age for sleep duration and number of night awakenings.	111
Table 20: Summary of Hierarchical Regression Model testing the moderating effect of reactivity and gender on the association between antenatal depression and infant sleep at 24 months of age for sleep duration and number of night awakenings.	113
Table 21: Comparison of demographic characteristics of the current sample (n=5,409) and the whole ALSPAC sample (n=14,062)	139
Table 22: Descriptive statistics for antenatal depression and Genotype frequencies for 5-HTTLPR including the A/G SNP (n=5,084).	142
Table 23: Descriptive statistics for total sleep time and awakenings by genotype and gender at 6 months of age	144
Table 24: Descriptive statistics for sleep variables by genotype and by gender at 18 months of age.	145
Table 25: Descriptive statistics for sleep variables at 30 months by genotype and by gender.	146
Table 26: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on the association between antenatal depression and a) sleep time and b) number of awakenings at 6 months, Step 4.	150
Table 27: Summary of Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on the association between antenatal depression and a) total sleep time, b) awakenings and c) sleep problems at 18 months, Step 4.....	151
Table 28: Summary of Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR on antenatal depression and a) sleep duration, b) awakenings and c) sleep problems at 30 months of age, Step 4.....	152
Table 29: Comparison of demographic characteristics of sub-sample with genetic data available with total Generation R sample.	156
Table 30: Descriptive statistics for antenatal depression and Genotype frequencies for 5-HTTLPR, n=3,366.....	159
Table 31: Descriptive statistics for infant sleep at 6 months of age by genotype and by gender.	160
Table 32: Descriptive statistics of Infant Sleep at 24 months of age by genotype and by gender.	161
Table 33: Summary of Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on the association between antenatal depression and i) sleep	

duration, ii) night awakenings. Coefficients for Step 1,2 & 3 are after inclusion of 3-way interaction term in Step 4.	163
Table 34: Summary of Hierarchical Regression Analysis for infant sleep duration and awakenings at 24 months of age. Coefficients for Step 1,2 & 3 are after inclusion of 3-way interaction term in Step 4.....	165
Table 35: Demographic characteristics of Study.....	183
Table 36: Descriptives of infant sleep at 5 months by actigraphy.....	196
Table 37: Descriptives of infant sleep at 5 months by maternal report	197
Table 38: Unadjusted bivariate associations of maternal depressive symptoms in the antenatal and postnatal periods with infant sleep assessed through actigraphy.	199
Table 39: Unadjusted bivariate associations of depressive symptoms in the antenatal and postnatal periods with infant sleep assessed through maternal report.	200
Table 40: Unadjusted bivariate associations between sleep variables as measured by actigraphy and maternal report (n=14).	204
Table 41: Descriptives for maternal cognitions.....	205
Table 42: Unadjusted bivariate associations between maternal cognitions and depressive symptoms.	206
Table 43: Descriptives for infant temperament scores.	207
Table 44: Unadjusted bivariate associations between maternal depressive symptoms and infant temperament	208
Table 45: Descriptives for infant cortisol at 5 months of age and maternal cortisol ante- and postnatal.	209
Table 46: Unadjusted bivariate associations maternal depressive symptoms and infant cortisol.	210
Table 47: Descriptives for maternal antenatal and postnatal sleep as assessed through the PSQI and actigraphy.	212
Table 48: Unadjusted associations between antenatal and postnatal maternal sleep.....	216
Table 49: Demographic characteristics presented by treatment arm (adapted from (Burns et al., 2013))	232
Table 50: Descriptive statistics for depression scores.	241
Table 51: Descriptive Statistics for Infant Sleep and Temperament presented by treatment arm and test statistics to examine differences between the two groups.	241
Table 52: Unadjusted associations between change in depression scores during pregnancy, infant temperament and sleep.	243
Table 53: Unadjusted associations between posntatal depression, infant sleep and temperament.	246

Table 54: Differences in change in depression scores, temperament and sleep duration by i) maternal SSRI use and ii) by feeding mode.	248
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LIST OF FIGURES

Figure 1: Schematic diagram of Hypothalamic-Pituitary-Adrenal axis	25
Figure 2: Double plotted actograms (from Wulff, Dedek, & Siegmund, 2001, p. 533) consisting of 3 series of recordings (21 days each) during the 1 st to 3 rd week, 7 th to 9 th week and 13 th to 15 th week post birth in two boys.....	32
Figure 3: Illustration of a) diathesis-stress model (left) and b) differential susceptibility theory (right) (an adaptation from Bakermans-Kranenburg and Van IJzendoorn's (2007, pp. 1167, FIGURE 1).	64
Figure 4: Steps for testing differential susceptibility from Belsky, Bakermans-Kranenburg and Van IJzendoorn (2007, pp. 302, BOX 1).	65
Figure 5: Diagram to represent attrition of data at each time point in the ALSPAC cohort.....	77
Figure 6: Schematic diagram of moderator analysis	83
Figure 7: Association between antenatal depression and infant sleep a) night awakenings and b) sleep problems in boys and girls, moderated by reactivity, using standardized residual scores, EPDS cut-off used >12 for Depressed vs. Not depressed.....	95
Figure 8: Association between antenatal depression and infant night awakenings at 30 months in boys and girls moderated by reactivity, using standardized residual scores, EPDS >12 for Depressed vs. Not depressed.....	98
Figure 9: Diagram to illustrate attrition of data at each time point in the Generation R cohort.	103
Figure 10: Association between antenatal depression and infant sleep duration in boys and girls, moderated by reactivity in the Dutch/European sample, using standardized residual scores, Depressed category top 15% of scorers.....	114
Figure 11: Flowchart to display data attrition for genetic data analysis in the ALSPAC cohort.	137
Figure 12: Flowchart to illustrate attrition of genetic data in the Generation R cohort.	155
Figure 13: Linear Relations between antenatal depression and night awakenings at 24 months as a function of 5-HTTLPR for girls, Depressed category, top 15% of scorers.	166
Figure 14: Single plotted actogram of 11 days recorded from two infants 5 months postpartum.	201
Figure 15: Maternal antenatal, postnatal and infant morning cortisol levels.....	209
Figure 16: Single plotted actograms of two mother-infant dyads.	213
Figure 17: The mean ($\pm$ SE) values for all sleep parameters in the antenatal (striped column) and postnatal periods (solid columns) as assessed by actigraphy, paired-samples t-tests, *p<.05.....	214

Figure 18: Participant Flowchart adapted from (Burns, et al., 2013)	233
Figure 19: Flowchart of measures collected at each phase of the study.....	238
Figure 20: Scatter plots with regression lines a) of infant temperament with change in depression scores (n=25) and b) of infant temperament with change in depression scores by treatment arm CBT (n=14), Care as Usual (n=11).	244
Figure 21: Scatter plots with regression lines a) of infant sleep duration during the night with change in depression scores (n=25) and b) of infant sleep duration during the night with change in depression scores by treatment arm CBT (n=14), Care as Usual (n=11).	245

LIST OF ABBREVIATIONS

5-HT	Serotonin
5-HTP	Serotonin Transporter
5-HTTLPR	5-HydroxyTryptamine Transporter Gene-Linked Polymorphic Region
BSQI	Brief Sleep Quality Index
CBT	Cognitive Behavioural Therapy
CIS-R	Clinical Interview Schedule- revised version
CNS	Central Nervous System
<i>df</i>	degrees of freedom
DSM-IV	Diagnostic and Statistical Manual for Mental Disorders – 4 th edition
EEG	Electroencephalography
EPDS	Edinburgh Postnatal Depression Scale
GAD	Generalised Anxiety Disorders
GWAS	Genome Wide Association Analysis
GxE	Gene environment interaction
IBQ	Infant Behaviour Questionnaire
ICD-10	International Classification of Diseases and Related Health Problems (10 th edition)
ICQ	Infant Characteristics Questionnaire
IS	Inter-daily Stability
IV	Intra-daily Variability
<i>l</i>	long allele
L10, L5	Least active 10 hours, least active 5 hours
M	Mean
M10, M5	Most active 10 hours, Most active 5 hours
MCISQ	Maternal Cognitions about Infant Sleep Questionnaire
μ V	microvolts
<i>n</i>	Number of Participants
<i>N</i>	Number of Participants
nmol/l	Nano moles per Litre
NPCRA	Non-Parametric Circadian Rhythm Analysis
NREM	Non Rapid Eye Movement
<i>p</i>	Probability
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomised Controlled Trial
REM	Rapid Eye Movement
<i>s</i>	short allele
SCID	Structured Clinical Interview for DSM-IV
SCN	Suprachiasmatic Nucleus
SD	Standard Deviation
SE	Standard Error
SES	Socio-economic Status
SLC6A4	Serotonin transporter gene

SLC6A4	Serotonin Transporter Gene
SLEQ	Stressful Life Events Questionnaire
SNP	Single Nucleotide Polymorphism
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Re-uptake Inhibitors
STAI	State Trait Anxiety Inventory
SWS	Slow Wave Sleep
t	t-statistic
TAU	Treatment as Usual
WHO	World Health Organization
YLD	Years Lost in Disability
β	Standardized beta coefficient
χ^2	Chi-Square Statistic

Chapter 1 Introduction

1.1 ANTENATAL DEPRESSION

Depression is a significant worldwide health problem and one of the most commonly encountered psychiatric disorders. Currently, the World Health Organization (WHO) estimates it is the leading global cause of years lost in disability (YLD) for both males and females (Mathers, Fat, & Boerma, 2008). The lifetime prevalence of depression in the general population is estimated between 6 and 17%, although estimates for women during the childbearing years are higher (21%) compared to males (13%) (Health, 2007; Kessler, 2003; Kessler et al., 2003).

Major depression, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), is evident when an individual experiences a minimum of two weeks of depressed mood or loss of interest, concurrent with other symptoms such as psychomotor agitation, disruption of appetite and sleeping habits, feelings of worthlessness or suicidality (American Psychiatric Association, 1994).

It often occurs concurrently with other psychiatric disorders, with nearly half of affected individuals also meeting criteria for general anxiety disorder (GAD) or substance abuse (Kessler, 2003; Kessler, et al., 2003; Regier, Rae, Narrow, Kaelber, & Schatzberg, 1998).

Depression during the perinatal period has an estimated prevalence of around 11% during pregnancy and 12% postnatally (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; Gaynes et al., 2005; O'Hara & Swain, 1996). Untreated antenatal depression has also been established as a predictor of postnatal depression with up to 45% of those experiencing depression in the postnatal period having also suffered from antenatal depression (Evans, Heron J., Francomb H., Oke S., & Golding J., 2001; O'Connor, Heron, Golding, Glover, & ALSPAC, 2003).

Depression is also known to interfere with one's ability to function and to fulfil social roles. This may be of particular importance during the ante- and postnatal periods as poor concentration, preoccupation and rumination may interfere with a woman's ability to provide optimal care for a new baby (O'Mahen, Flynn, & Nolen-Hoeksema, 2010). Depression specifically during the antenatal period may also impact on child development first, by interfering with a woman's preparation for motherhood (Pearson, Cooper, Penton-Voak, Lightman, & Evans, 2010; Pearson et al., 2013; Pearson et al., 2012), and second, through depression-related changes to maternal physiology which

may have an effect on fetal development (Glover, O'Connor, & O'Donnell, 2010; O'Donnell, O'Connor, & Glover, 2009).

1.1.1 Antenatal depression & child development

A large body of evidence from research in both animals and humans suggests that experiences occurring early in life (including those in utero) may result in adult disease. Some well-documented examples include cardiovascular disease and diabetes mellitus (Barker, 2001; Gluckman & Hanson, 2005, 2006).

There is also accumulating evidence to suggest that disturbances in maternal mental health may have long-lasting effects on a child's development (Deave, Heron, Evans, & Emond, 2008; Pawlby, Sharp, Hay, & O'Keane, 2008; Van den Bergh & Marcoen, 2004). Research in this field has often used the terms 'anxiety', 'depression' and 'stress' interchangeably to reflect a disturbance in maternal stress. This is partly due to the large co-morbidity between depression and anxiety and partly due to the common mechanisms hypothesized to be involved in the transmission of risk from mother to offspring.

During pregnancy, fetuses of women with antenatal depression have been shown to spend more time in an active state. They also show an increase in heart rate following a habituation paradigm compared to fetuses of non-depressed women who show a decrease in heart rate (Dieter et al., 2001; Emory & Dieter, 2006; Field, 2011).

Antenatal depression has also been associated with pregnancy complications and adverse birth outcomes such as pre-term labour, low birth weight and being born small for gestational age (Alder, Fink, Bitzer, Hosli, & Holzgreve, 2007; Field, 2006; Grote et al., 2010; Lundy et al., 1999b). A recent meta-analysis of pregnancy complications and obstetric measures suggests a relative risk of 1.13 for preterm birth, 1.18 for low birth weight and 1.03 of intra-uterine growth restriction. This meta-analysis also suggests that relative risks vary according to the measures used for classification of depression and the location of the study, with categorical measures of depression yielding a higher effect size. A larger effect size was also found for studies conducted in developing countries (Grote, et al., 2010). Some studies also show neonates of depressed mothers to have elevated heart rate, to perform less optimally on the Neonatal Behavioural Assessment Scale (NBAS) and to show less positive affect (Field, 2006; Lundy, et al., 1999b).

Infants of antenatally depressed women have been reported to cry more at 3 months of age and to have more difficult temperament (DiPietro, Ghera, & Costigan, 2008; McGrath, Records, & Rice, 2008; Milgrom, Westley, & McCloud, 1995). Antenatal depression has also been associated with poorer cognitive and language development in children (Van den Bergh, Mulder, Mennes, & Glover, 2005), as well as with an increased risk of emotional and behavioural problems in the offspring at 4 and 7½ years of age and antisocial behaviour at age 16 (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; Deave, et al., 2008; Hay, Pawlby, Waters, Perra, & Sharp, 2010; Luoma, Tamminen, & Koivisto, 2004; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; O'Connor, et al., 2003; Pawlby, Hay, Sharp, Waters, & O'Keane V, 2008; Van den Bergh, et al., 2005). Antenatal depression was also associated with higher risk of maltreatment by age 11 and a higher risk of psychopathology in adolescence (depressive disorder or conduct disorder). Exposure to both antenatal depression and maltreatment was associated with an 11-fold risk increase in offspring psychopathology (Pawlby, Hay, Sharp, Waters, & Pariante, 2011). More recently, antenatal depression has been associated with infant sleep problems (Armitage et al., 2009; Baird, Hill, Kendrick, & Inskip, 2009; Diego, Field, & Hernandez-Reif, 2005; Field et al., 2004; Field et al., 2007; Jones, Field, Fox, Lundy, & Davalos, 1997; Nevarez, Rifas-Shiman, Kleinman, Gillman, & Taveras, 2010; O'Connor, 2007). A more detailed discussion of these studies can be found in Section 1.3 of this chapter.

The effects of antenatal depression on child development are complex, but have been attributed in part to the “programming effects” of antenatal depression on the developing fetus.

1.1.2 Fetal Programming & The developmental origins of health and disease

The fetal programming hypothesis has been used to explain fetal adaptations to environmental cues with the aim of enhancing survival (Gluckman, Hanson, Spencer, & Bateson, 2005). Such plasticity aims to assist the individual to adapt to environmental cues in anticipation of what the environment post birth will be. Also known as the predictive adaptive response, this process, from an evolutionary perspective, aims to provide the individual with a developmental advantage (Glover, 2011). These

adaptations may increase chances of survival; however, at the same time, they may place the organism at risk of a number of other conditions, as adaptations may be at the expense for example, of the development of another organ. Changes during “*sensitive*” periods of development may have long-lasting effects and influence the risk of chronic disease (even into adult life) (Schlotz & Phillips, 2009). In addition, if the forecast of the environment proves to be wrong for instance, due to a change of circumstances, then the adaptations may even prove harmful for the child.

A well-studied example is that of body weight at birth. If the fetus experiences malnutrition, it may adapt its body size (and wider physiological development) to increase chances of survival in an environment where nutrition is scarce. If the child however, is born in an environment with access to adequate nutrition, the individual may be at higher risk for Type II diabetes and cardiovascular disease in later life. David Barker and colleagues first identified this association between low birth weight and an increased risk of cardiovascular disease in the UK (Barker & Osmond, 1986). This work brought to scientific attention the possibility that early environmental exposures may affect later trajectories of health and disease. Their work and the numerous replications, which followed, led to the theory of developmental origins of health and disease (DoHad). It postulates that “*an altered long-term risk of disease is initially induced through adaptive responses that the fetus or infant makes to cues from the mother about their health or physical state*” (p. 62, Gluckman, Hanson, Cooper, & Thornburg, 2008). Responses may include changes in hormone production, metabolism and tissue sensitivity to hormones.

1.1.3 Mechanisms through which antenatal depression affects child development

There are a number of proposed mechanisms through which antenatal depression is hypothesized to impact fetal development. These include the Hypothalamic Pituitary Adrenal (HPA) axis, the role of the placenta, and the contribution of genes in the heritability of stress responses and epigenetic mechanisms. There is limited evidence as to what the exact mechanisms may be, however, there is accumulating evidence for some of these potential pathways, most notably the HPA axis, the operation of which is described in more detail below.

Additional but not necessarily contradictory mechanisms include high-risk behaviours such as smoking and alcohol consumption during pregnancy. Women who suffer from antenatal depression have been reported to have higher levels of smoking and alcohol consumption during pregnancy, which may independently affect fetal development (Barr et al., 2006; Streissguth et al., 1994; Testa, Quigley, & Eiden, 2003). Furthermore, they are also at higher risk of receiving insufficient antenatal care and to have a less healthy diet (Lindgren, 2001). Both factors have been independently associated with poor fetal development.

The HPA axis

One key biological pathway implicated in the fetal programming model of antenatal depression is the hypothalamic pituitary adrenal axis (HPA) (Bergman, et al., 2007). The HPA is the principal response system to stress and activates what is known as the fight or flight response but is also important in supporting normal physiological functioning. The end product of the HPA axis, cortisol, is released during stressful situations (see Figure 1). Cortisol regulates the effect of the HPA axis, thus ensuring that the body does not overreact in response to stress. In addition to these short-term fluctuations in cortisol throughout the day, cortisol is under circadian regulation with highest levels in morning before awakening and lower levels during the middle of the night.

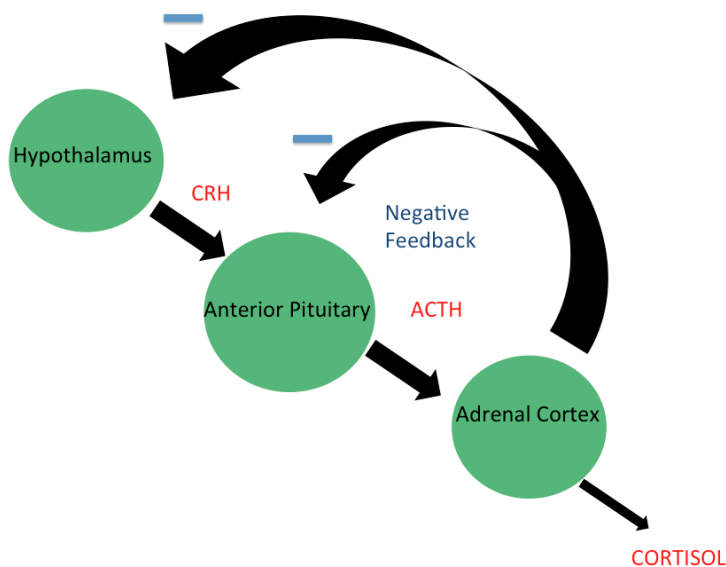


Figure 1: Schematic diagram of Hypothalamic-Pituitary-Adrenal axis

Decades of research in animals have demonstrated long-term behavioural and neurobiological effects in the offspring of antenatally stressed animals, with marked effects on the HPA axis (Monk, Spicer, & Champagne, 2012; Weinstock, 2005, 2008). It is hypothesised that maternal depression exposes the fetus to higher levels of glucocorticoids, thus altering the development and regulation of the infant's HPA axis. Changes in circadian cortisol rhythm may in turn affect regulation of sleep-wake rhythms in infants (Lee & Rosen, 2012). Antenatal stress in rodents and non-human primates has been associated with altered behaviour and cognitive functioning, with associated down-regulation of glucocorticoid (GR) receptors in the hippocampus and the hypothalamus (Barbazanges, Piazza, Le Moal, & Maccari, 1996; Chapillon, Patin, Roy, Vincent, & Caston, 2002; Schneider, Moore, Kraemer, Roberts, & DeJesus, 2002; Weinstock, 1997; Weinstock, 2001).

Exposure to antenatal stress has been shown to alter the functioning and responsiveness of the child's HPA system. For example, children of antenatally depressed mothers were reported to have higher baseline cortisol levels during infancy and at 10 years of age, as well as higher levels of cortisol reactivity (O'Connor et al., 2005). More recently Glover and colleagues (2009) have also reported cortisol differences in the intra-uterine environment, with higher levels of cortisol in the amniotic fluid found in stressed pregnant women.

Higher levels of cortisol in the intra-uterine environment have been hypothesized as the key mechanism. The increased activation of maternal HPA axis due to the depressive symptoms is hypothesized to cause an increase in maternal cortisol levels, which in turn may affect fetal development by crossing the placenta (Wadhwa et al., 2004; Wadhwa, Sandman, Chicz-Demet, & Porto, 1997; Wadhwa, Sandman, & Garite, 2001). A placental enzyme known as 11 beta hydroxysteroid dehydrogenase Type II, (11 β HSD2) metabolizes cortisol into cortisone. It is estimated that only 20% of cortisol in its original form reaches the fetus (Gitau, Fisk, & Glover, 2001; Gitau, Fisk, Teixeira, Cameron, & Glover, 2001). It has been suggested however, that in antenatally stressed pregnant women there may be a down-regulation of 11 β HSD2, which could allow for higher levels of cortisol to cross the placenta, a finding that has been confirmed in rats (Mairesse et al., 2007; O'Donnell et al., 2012). This in combination with higher levels of corticotropin releasing hormone (CRH) also found in the intra-uterine environment

of stressed women, may significantly affect the development of the fetus; in particular, areas such as the hippocampus, which have a high density of CRH receptors (Glover, et al., 2009; Sandman, Wadhwa, Chicz-DeMet, Porto, & Garite, 1999; Sandman et al., 1999). This is currently supported by animal work in the hippocampal pyramidal cells and by elevated levels of adrenocorticotrophic hormone (ACTH) and cortisol (both baseline and reactivity) in rodents (Talge, Neal, & Glover, 2007).

The HPA axis has long been implicated in the aetiology of depression in adult life. A recent meta-analysis suggested that patients with depression had higher cortisol levels during the recovery period from stress compared to controls (Burke, Davis, Otte, & Mohr, 2005). The authors also reported a time of day effect, where afternoon studies were more likely to report higher baseline cortisol levels, blunted stress reactivity, and impaired recovery in depressed patients.

Although much remains to be understood about the role of the HPA axis in the transmission of risk, evidence is accumulating from animal and human studies, that it is a key potential pathway by which antenatal stress may influence offspring development.

1.2 INFANT SLEEP

In seeking to understand how antenatal depression may affect the earliest aspects of child development, we are hampered by difficulties in accurately and reliably assessing emotional and behavioural states in very young children. One of the earliest markers of this kind of biobehavioural development is the development of regulated sleep patterns. As well as this sleep performs a critical set of developmental tasks, sleep is the state in which the infant exists for the majority of its early life. This section describes various aspects of sleep in young children. It will start with a brief introduction to sleep in adults. This will serve as a point of reference to better illustrate how sleep develops and how it is different to adult sleep. This will be followed by a description of sleep characteristics in three age groups (in utero, from 0-12 months, and 1-5 years of age).

The section after this describes why sleep is imperative for brain maturation and development. Here, evidence will be discussed regarding disturbances in sleep during early life can affect learning, cognitive functioning, and emotional and behavioural problems. This section continues with a brief discussion of the genetic and environmental determinants of sleep and concludes with a comparison of different methodologies used to assess sleep.

1.2.1 Brief Introduction to Sleep

1.2.1.1 *The Two Process Model*

There are two processes that regulate the sleep and waking states: the homeostatic drive, which facilitates the appropriate duration of sleep and the circadian drive, which facilitates the appropriate timing of sleep and wakefulness across the 24 hour day-night cycle (Lockley & Foster, 2012).

During the homeostatic process, also termed Process S, a need for sleep accumulates during wakefulness and is satisfied during sleep (Peirano, Algarín, & Uauy, 2003). During sleep the pressure dissipates until it becomes low enough to wake up.

Sleep propensity is also regulated by the circadian pacemaker (also termed the master circadian clock), which in mammals is located in the suprachiasmatic nuclei (SCN), a pair of nuclei containing approximately 10,000 neurons in the anterior hypothalamus (Lockley & Foster, 2012; Roenneberg & Mellow, 2005). The circadian pacemaker generates 24-hour rhythms endogenously, which regulate the timing of a number of

behavioural, physiological and metabolic functions; for example production of hormones, including melatonin and cortisol, temperature regulation and glucose and insulin levels (Lockley & Foster, 2012). The endogenous rhythms are synchronized to environmental cues, also referred to as zeitgebers, the most important of which is the light/dark cycle. Photoreceptors in the eye (rods, cones and melanopsin-containing retinal ganglion cells) receive the zeitgeber light which is then transferred via the retino-hypothalamic tract to the SCN. The 24-hour rhythm of sleep and arousal as determined by the circadian pacemaker is termed Process C (Lockley & Foster, 2012).

Unlike Process C, where the anatomical location of the circadian clock is well established, the location and substances involved in the homeostatic drive are poorly understood (Lockley & Foster, 2012).

1.2.1.2 The Stages of Sleep

The sleep cycle consists of two types of sleep, rapid eye movement sleep (REM) and non-rapid eye movement sleep (NREM) which alternate to form a REM-NREM cycle which lasts 80-110 minutes (Wulff, Porcheret, Cussans, & Foster, 2009). An individual will usually go through 4 or 5 REM-NREM cycles during the night depending on sleep duration.

The distinct phases of sleep can be observed using electroencephalography (EEG). NREM Stage 1 occurs at the beginning of sleep and is characterized by small amplitude waves with irregular frequency as well as sharp waves called vertex spikes. NREM Stage 2 is characterized by theta waves of 4-8 Hz, waves, also known as sleep spindles between 12 and 14 Hz, which occur periodically in bursts as well as high amplitude and low frequency events also known as K complexes.

NREM stages 3 and 4 are also referred to as slow wave sleep (SWS) due to the presence of delta waves, which are slow, large amplitude waves. Stage 3 is followed by Stage 4, during which an increase in the percentage of time spent in delta waves occurs. REM sleep begins after Stage 4. This stage is different to the aforementioned 4 stages and is characterized by EEG patterns similar to those during waking, such as alpha and beta waves, rapid eye movements and a loss of muscle tone.

1.2.2 Sleep development in children

Sleep is one of the primary brain activities and during infancy more time is in fact spent sleeping than awake. Mindell and Owens (2003) reported that nearly 2/3 of a newborn's

day is spent sleeping and by the end of infancy this has decreased to half of the day. It is striking to consider that by the age of 3 the average child will have spent more of his/her time asleep than in all wakeful activities (Heraghty, Hilliard, Henderson, & Fleming, 2008; Wiggs, 2007).

Normal variations exist in the sleep characteristics of the general population, for example in quantity and quality of sleep, and ease of initiating and maintaining sleep.

1.2.2.1 In utero

The mechanisms involved in the regulation of sleep-wake behaviour develop during life in utero, although it remains to be determined whether the fetus is truly awake at this point (WHO, 2004). Through ultrasonography it has been possible to establish that as early as 8 to 12 weeks gestation the fetus has a repertoire of spontaneous movements. Patterns of fetal movement are followed by periods of quiescence (Hoppenbrouwers, Ugartechea, & Combs, 1978; Peirano, et al., 2003).

By week 20 and continuing to week 28 a rhythm starts to form which is characterized by periods of silence with no evidence of respiratory movement at this point (Dawes, Fox, Leduc, Liggins, & Richards, 1972). From week 24 onwards development of the cochlea and peripheral sensory organs allow for reaction to external noises.

At 30 weeks gestation sleep accounts for 53% of the time and may rise to 60% closer to term (WHO, 2004). From this point onwards, fetal heart rate is synchronized with a number of the mother's rhythms including heart rate, temperature and melatonin rhythms. As the fetus develops so does the central nervous system (Lockley & Foster, 2012) and synchronization between cyclic activity and changes in heart rate and eye movement are observed (Peirano, et al., 2003; Swartjes, Van Geijn, Mantel, Van Woerden, & Schoemaker, 1990; Visser, Poelman-Weeshes, Cohen, & Bekedam, 1987). As early as 32 weeks distinct episodes of sleep have been identified; quiet sleep (equivalent to NREM), active sleep (equivalent to REM) and intermediate sleep.

1.2.2.2 From birth to 12 months of life

Newborns will spend about 16 to 17 hours a day sleeping and this will decrease to about 14 or 15 hours a day by 16 weeks of age (WHO, 2004). Patterns of sleep/wake though will vary greatly between infants (for example of variability see actograms Figure 2). Processes S and C start functioning rhythmically early on and the clock produces a non-

24-hour sleep/wake pattern (Lockley & Foster, 2012). Evidence from pre-term infants suggests that early exposure to the light/dark cycle has beneficial effects in terms of increased sleep and growth and in the development of circadian rhythms of heart rate, skin temperature and potentially melatonin rhythm (Mirmiran, Maas, & Ariagno, 2003). Research in baboons suggests that as early as 125 days in prematurely born baboons the biological clock is responsive to light; if extrapolated to humans this could suggest that as early as 28 weeks gestation, infants may be responsive to the effects of light on the circadian system (Mirmiran, et al., 2003). From around 4 to 6 weeks of age post birth, sleep and the feeding schedule are primed by the light-dark cycle and sleep is more consolidated with longer sleeping periods during the night and regular awakenings during the early hours of the daytime. Total sleep time continues to decrease as newborns develop and by about 6 months of age sleep will occupy 13 to 14 hours of each 24 hours (Parmelee, Wenner, Akiyama, Schultz, & Stern, 1967). Between the ages of 2-6 months of age, a more distinct 24-hour cycle emerges with distinct prolonged sleeping periods over the night and naps during the day. This rhythm continues to consolidate between 6 and 12 months of age.

During the first 6 months three distinct sleep phases become recognisable (Active, Quiet and Indeterminate sleep). These are identified through a combination of respiration, heart rate EEG and behavioural data. At this stage REM and NREM, although present, are not sufficiently organized identifiable states (de Weerd & van den Bossche, 2003). Active Sleep consists of continuous electrophysiological activity throughout the neocortex. Depending on whether it precedes or succeeds quiet sleep, active sleep can reach up to 70 μ V or between 20 μ V and 50 μ V respectively (Gomez, Newman-Smith, Breslin, & Bootzin, 2011). Quiet sleep is distinguished from active sleep due to the background pattern of “noise” with sporadic “bursts” of delta and theta waves (which can reach amplitudes of 200 μ V). Periods of alpha and beta waves are also present during this period of quiet sleep. The last phase, known as indeterminate sleep, consists of disorganized EEG patterns and occurs between Active and Quiet sleep (Gomez, et al., 2011). REM and NREM sleep develop between 6 months and 1 year of age. NREM develops from Quiet sleep. By 1 year of age sleeping periods during the night will have reached 8 to 9 hours (Anders & Keener, 1985).

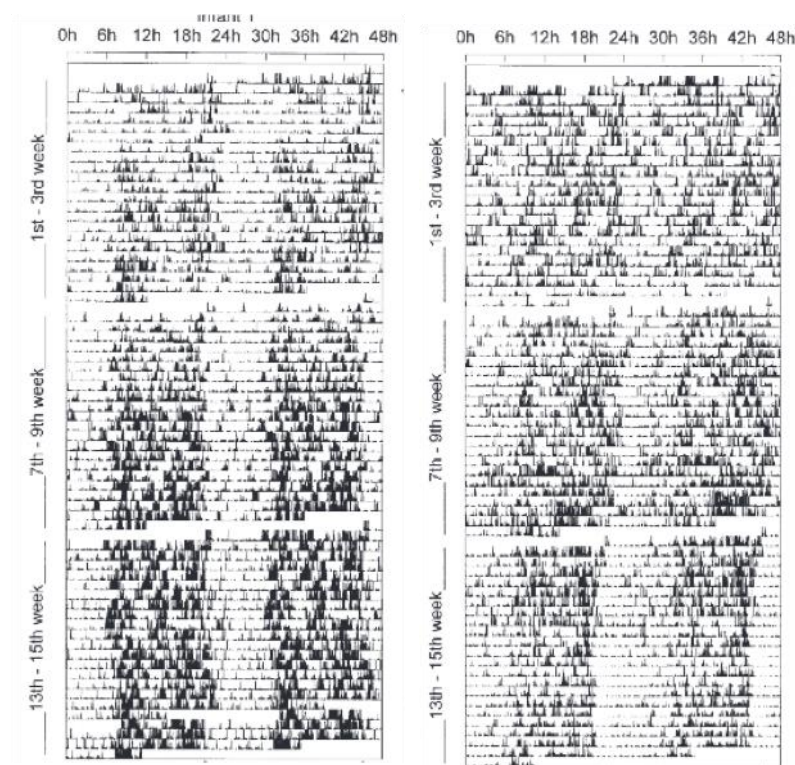


Figure 2: Double plotted actograms (from Wulff, Dedek, & Siegmund, 2001, p. 533) consisting of 3 series of recordings (21 days each) during the 1st to 3rd week, 7th to 9th week and 13th to 15th week post birth in two boys.

Nighttime awakenings during the first year of life are an important and regularly assessed aspect of infant sleep both because they affect parents' life as well as being identified as an indicator of disturbed sleep. Anders and Keener (1985) distinguish between two types of night waking - infants who despite waking up are able to soothe themselves back to sleep quietly, and those who cry to attract parental attention and who are labelled night-wakers. It is reported that by 2 months of age approximately 44% of infants will be sleeping through the night (Anders & Keener, 1985). The same authors suggest that from 6 to 12 months of age night waking might increase. As infants develop, daytime naps will also become more consolidated and will decrease from about 3-4 at 6 months of age to 2 naps by 9-12 months of age. Disrupted sleep is viewed as a regulatory problem, particularly in the first year of life. Infants with regulatory problems may also present with difficulties in feeding, fussiness and irritability, or difficulty

adapting to change (Hemmi, Wolke, & Schneider, 2011). These same infants tend to cry longer and need more time to settle back into sleep despite assistance from the caregiver.

1.2.2.3 1-5 years of age

Between 1 and 5 years of age children's sleep continues to become more similar to adult sleep. During preschool years total sleep time continues to decline from about 15 hours a day at 1 year of age, to 13-14 hours at 2 years of age, to 12 hours by 4 years of age. Nighttime sleep progressively becomes more consolidated and lasts about 10 hours (Kohler, 1968) and a reduction in daytime sleep occurs. Between the ages of 0-3 years naps typically occur during the mid-morning and early afternoon, which will gradually disappear between the ages of 3 and 5 years. The NREM-REM cycle will also increase from about 60 minutes at 1 year of age to 75 minutes at 2 years of age and finally mirror that of adult sleep lasting about 90 minutes by 6 years of age. Time spent in slow wave sleep (SWS) and REM sleep also decreases.

1.2.3 Why is sleep an important aspect of child development

There are two proposed mechanisms through which disrupted sleep can affect child development. The first suggests that disrupted sleep causes daytime sleepiness and therefore reduced alertness (Frank & Benington, 2006; Mirmiran, 1995; Mirmiran & Someren, 1993; Sadeh, 2007). This in turn affects daytime functioning compromising behavioural regulation and cognitive functioning. Early childhood is the period during which children learn to regulate their emotions and significant sleep disruptions may affect this process (Dahl & Harvey, 2007). Furthermore, Sadeh et al. (2003a) reported sleep to affect attention, memory, concentration and reaction times in children, with younger aged groups affected disproportionately compared to older groups.

The second mechanism is based on the role of sleep in brain maturation. Disrupted or insufficient sleep for example, disrupted REM sleep, will reduce the activities required for brain maturation, memory consolidation and learning (Harrison & Horne, 2000; Sadeh, 2007). During the first years of life, the sleep-wake rhythm undergoes substantial developmental changes as a result of brain maturation and further development of the Central Nervous System (CNS). The most dramatic changes for both the CNS and sleep-wake rhythm occur during the first two years of life, suggesting that any disruptions to the processes at this stage may have long-lasting consequences. These two on-going processes seem to be interdependent. For example, brain plasticity, which refers to the ability of the brain to adapt to environmental cues both structurally and functionally, seems to be negatively affected in REM and NREM sleep-deprived animals, resulting in diminished learning, long-term behavioural effects and smaller brain size (Ednick et al., 2009). REM sleep is also understood to be essential for endogenous stimulation of neuronal systems. This endogenous stimulation refers to discharges from neurons within the neurosensory system which seem to be important for axon growth and targeting, creating connections between sensory organs and brain structures (e.g. visual, olfactory and limbic systems). In newborns, REM sleep occupies more than half of sleep time. This period is characterised by a high level of endogenous neuronal activation both in terms of duration and intensity. As the infant brain continues to mature, the high amount and intensity of this neuronal activation starts to diminish. It is also hypothesised that sleep spindles and K-complexes may be particularly important in terms of brain maturation particularly regarding the development of the cerebral cortex and processes involving memory and learning. Research in animals who had

experienced REM sleep-deprivation during the neonatal period suggests increased levels of disturbed sleep and increased anxiety during adulthood, thus, indicating that disturbances during early childhood may have effects lasting into adulthood (Mirmiran, Van de Poll, Corner, Van Oyen, & Bour, 1981)

This evidence suggests that sleep disturbances in early childhood might be more detrimental than disturbances in adulthood, further highlighting the need for more research in the effects of sleep disruption in children.

1.2.3.1 Sleep, Cognition and Language

There are numerous studies, which examine cross-sectionally the association between sleep and cognitive performance (for reviews see Bub, Buckhalt, & El-Sheikh, 2011; Dewald, Meijer, Oort, Kerkhof, & Bögels, 2010). There are, however, few studies, which examine this association among infants or pre-schoolers and even fewer which examine this association longitudinally.

Scher (2005) reported that more consolidated sleep, less motor activity during sleep and fewer arousals, as measured by actigraphy, were associated with higher cognitive achievement using the Bayley Scales of Infant Development in a sample of low risk 10 month old infants. Bernier et al. (2010) reported sleep in 1 year old children was associated with executive tasks at 18 months and 2 years of age, whilst controlling for cognitive ability. These findings held at 4 years of age: children getting higher proportions of their sleep during the night performed better in executive functions and this association held whilst controlling for prior cognitive functioning and socioeconomic status (Bernier, Beauchamp, Bouvette-Turcot, Carlson, & Carrier, 2013). Dearing et al. (2001) reported better circadian regulation at 7 and 19 months of age to be associated with higher cognitive and language achievements at 24 and 36 months respectively. Touchette et al. (2007) reported that sleep time reduction by one hour in children younger than 3 ½ years of age was associated with cognitive performance at 6 years of age. Dionne et al. (2011) in a sample of 1029 twins reported that day/night sleep ratio at 6 months was 64% heritable and predicted language skills at 18 and 30 months of age. Sleep at 18 months of age predicted language at 60 months of age.

A recent meta-analysis in children aged between 5-12 years of age reported that sleep duration was significantly and positively associated with cognition and more

specifically with executive functioning, multiple-domain cognitive functioning and school performance (Astill, Van der Heijden, Van IJzendoorn, & Van Someren, 2012). This meta-analysis also examined variables that may affect the precision of measurement of the sleep duration. The authors reported that larger effect sizes were apparent in the association between sleep and cognition when actual sleep time compared to total sleep period in bed was used. Interestingly this meta-analysis did not find a significant association between sleep efficiency and cognition or between sleep (both duration and efficiency) and memory.

1.2.3.2 Sleep and Emotional and Behavioural Problems

Studies examining the association between sleep and emotional functioning suggest that disturbed sleep is associated with mood and anxiety disorders (Alfano, Beidel, Turner, & Lewin, 2006; Hudson, Gradisar, Gamble, Schniering, & Rebelo, 2009; Johnson, Roth, & Breslau, 2006). In pre-school children frequent night-waking and bed resistance have been associated with internalising and externalising problems (Lam, Hiscock, & Wake, 2003; Reid, Hong, & Wade, 2009).

Gregory and colleagues (2005; 2004) examined 943 children as part of the Dunedin Multidisciplinary Health and Development Study and found parental-reports of sleep problems at 3 to 4 years of age to predict anxiety at age 7, and sleep problems at years 5,7, and 9 of age to predict anxiety at 21 and 26 years of age. These associations held after controlling for internalizing problems, gender, and socioeconomic status. Parental reports of shorter sleep duration in children compared to their peers were associated with higher risk for depression and anxiety (Fredriksen, Rhodes, Reddy, & Way, 2004; Smaldone, Honig, & Byrne, 2009), for example in a longitudinal community study in The Netherlands, 2,076 children between the ages of 4-16 years of age who were rated by their parents as sleeping less than their peers scored higher on the Anxious/Depressed scale and the Aggressive Behaviour Scale on the Child Behaviour Checklist (Gregory, et al., 2004).

A recent meta-analysis reported that sleep duration but not efficiency was related to internalizing problems, however, due to the small number of studies the findings should be interpreted cautiously (Astill, et al., 2012). It is also important to note here that in correlational and observational studies such as the ones discussed in this section the association between emotional functioning and sleep can often be bi-directional with

internalizing problems also negatively impacting on sleep (Lund, Reider, Whiting, & Prichard, 2010).

In terms of behavioural problems a widely assessed association is that of infant sleep and attention regulation and problems (Sadeh, 2007). Attention problems in children with disrupted sleep have been reported in a number of studies (Dahl, 1996; Dahl, Pelham, & Wiersen, 1991). More specifically, in experimental studies both acute sleep restriction and moderate accumulated sleep restriction were associated with attention difficulties; concentration problems were more evident in children who were getting up earlier and were receiving less sleep (Epstein, Chillag, & Lavie, 1998; Fallone, Acebo, Arnedt, Seifer, & Carskadon, 2001; Fallone, Acebo, Seifer, & Carskadon, 2005).

Behavioural problems have been associated with disrupted sleep in a series of studies in healthy children (Hiscock, Canterford, Ukoumunne, & Wake, 2007; Lam, et al., 2003; Morrison, McGEE, & Stanton, 1992; Sadeh, Gruber, & Raviv, 2003b; Zuckerman, Stevenson, & Bailey, 1987). In a 4-year follow up of 470 Finnish children, persistent sleep problems were associated with a 16 fold risk of psychosocial symptoms and more specifically, aggression, social and attention problems and anxious or depressed mood (Simola, Liukkonen, Pitkäranta, Pirinen, & Aronen, 2012). In a large sample of $n=3,000$ of 2-3 year olds, Reid and colleagues (2009) reported that maternally rated sleep problems, relating to getting to or staying asleep, accounted for a small but independent portion of the variance in both internalizing and externalizing behaviours.

A recent meta-analysis reported shorter sleep duration but not efficiency to be associated with externalizing behaviour (Astill, et al., 2012). The authors further reported a highly significant effect size in studies using actigraphy in contrast to studies using polysomnography in which this association was not found.

More research is needed to fully understand the short and long-term consequences of sleep disturbances on child development as well as the causal direction of this association. The current literature demonstrates an association between sleep problems and behavioural and emotional problems as well as cognitive development.

1.2.4 The aetiology of sleep-wake behaviour

In this section of the thesis, the various factors contributing to sleep are considered along with the different methodologies utilized to examine genetic and environmental influences on sleep patterns.

1.2.4.1 Heritability/Genes

Methodologies which are commonly utilized in animal research, such as gene mutations in drosophila or breeding of knockout¹ mice, are unavailable in research with humans for obvious ethical reasons (for a review of genetic approaches used in sleep research see Gregory & Franken, 2009). They do however, provide indispensable information, for example, Wisor and colleagues (2003) were able to exhibit the role of the serotonin transporter gene (SERT) in the regulation of REM sleep when higher rates of REM sleep were observed in SERT knockout mice compared to wild types.

For research with humans, twin studies provide a useful design and natural experiment to examine the aetiology of sleep. This design benefits from the two types of twins monozygotic (MZ), who share 100% of their genetic make-up and dizygotic (DZ) who share half of their segregating genes (and in genetic terms are similar to full siblings). These genetically sensitive designs, allow researchers to estimate the contribution of additive genetic, non-additive genetic, shared and non-shared environmental influence².

A large body of evidence demonstrates that many aspects of EEG and sleep are substantially genetically determined (for reviews see Andretic, Franken, & Tafti, 2008; Kimura & Winkelmann, 2007; Tafti & Franken, 2002). Studies which have used twins to assess the genetic contribution to sleep patterns and EEG have demonstrated that REM sleep is principally influenced by environmental influences, whilst delta wave sleep and slow wave sleep mostly genetically determined (Ambrosius et al., 2008; Linkowski, Kerkhofs, Hauspie, & Mendlewicz, 1991; Linkowski, Kerkhofs, Hauspie, Susanne, & Mendlewicz, 1989). A recent study by De Gennaro et al. (2008) reported that activity between 8-16 Hz during NREM showed a heritability estimate of 96%.

¹ Where a certain gene is abolished to observe to effect the absence of that gene on the phenotype

² Additive genetic influence: the cumulative genetic effect of genes on a given behaviour, non-additive genetic influences: the interaction of genes at a locus, shared environmental influences: influences which are shared between twins, non-shared environmental influences: influences which are unique to each twin

Studies examining sleep based on subjective reports suggest that 30-50% of the variance in subjective sleep quality is accounted for by genetic contributions (Heath, Eaves, Kirk, & Martin, 1998; Partinen, 1983). The results are analogous to other sleep patterns which were subjectively reported such as parasomnias and insomnias, sleep length, napping and sleepiness, sleep time, sleep onset latency and sleep disturbances (Heath, et al., 1998; Hublin, Kaprio, Partinen, & Koskenvuo, 2001; McCarren, Goldberg, Ramakrishnan, & Fabsitz, 1994; Partinen, 1983; Watson, Goldberg, Arguelles, & Buchwald, 2006). Data from the Washington Twin Registry, suggest that a third of the variance in sleep length was due to additive genetic effects as were sleep disturbances (Watson, Buchwald, Vitiello, Noonan, & Goldberg, 2010). Barclay et al. (2010) also demonstrated significant genetic effects with regards to sleep quality and diurnal preference (morning/evening type).

Fisher and colleagues (2012) in a large study of adolescents (n=1931 pairs of twins) demonstrated duration of daytime naps and nighttime sleep duration to be predominantly determined by the shared environment (66% and 57% respectively), with only a modest genetic effect (26% and 37% respectively).

A small number of studies were identified examining sleep patterns in children. Brescianini and colleagues (2011) examined 314 pairs of twins at 18 months of age and found substantial environmental contributions for nighttime sleep duration and diurnal sleep (64.1% and 61.2%). Nighttime awakenings were also substantially explained by environmental influences (63.2%) and about a third of the variance was explained by heritability (35.3%). Similar results emerged from a study of twins in Japan where 60% of differences in time to fall asleep were explained by shared environment and 32% by genetic factors (Ando et al., 2006). Finally, Gregory and colleagues (2006), in a sample of 330 pairs of twins 8 years of age, reported sleep difficulties to show some genetic influence although parental and child reports of sleep yielded different results with parental reports suggesting greater genetic influence, highlighting thus potential rater bias in the assessment of child sleep. The results should be interpreted cautiously as both studies were not powered to detect small effects.

Approaches used to investigate the influence of specific gene variants include linkage and association studies. Linkage studies consist of tracing back a disease or trait through long and large family pedigrees or more commonly pairs of affected siblings. The latter methodology allows for researchers to calculate the probability that a gene is linked to

a gene variant which in turn affects a particular disorder (Plomin, DeFries, McClearn, & McGuffin, 2008). This approach however also presents with disadvantages especially in the case of polygenetic influences or if the gene variant is rare in the population studied. Genome wide association studies (GWAS) are also emerging as a popular alternative allowing for the mapping of hundreds of thousands of polymorphisms and for identifying candidate genes.

Where candidate genes are already available association studies compare frequencies of the variant in the population with or without the trait (or with different levels of the trait i.e. high vs. low risk).

‘CLOCK’ genes are a group of genes which have been mostly examined as determinants of circadian phenotypes and include CLOCK, BMAL1, three Period genes (PER -PER1, PER2 and PER3) and two Cryptochrome genes (CRY - CRY1 and CRY2). CLOCK and BMAL1 regulates the expression of PER and CRY genes (Wulff, et al., 2009). Polymorphisms of the above mentioned genes have been associated with advanced sleep phase syndrome, delayed phase syndrome and diurnal preference (Allebrandt et al., 2010; Archer et al., 2003; Benedetti et al., 2007; Carpen, Von Schantz, Smits, Skene, & Archer, 2006; Ebisawa et al., 2001; Katzenberg et al., 1998; Serretti et al., 2003; Toh et al., 2001). They have also been associated with shorter sleep duration and delayed sleep onset in individuals with bipolar disorder, diurnal preference and sleep duration in the general population.

The serotonin transporter polymorphism (5-HTTLPR) gene has been a popular candidate gene in the area of sleep and more specifically in sleep quality. Recent investigations have reported a higher prevalence of the short allele (‘s’) in individuals with primary insomnia and decreased sleep quality in individuals dealing with chronic stress (Brummett et al., 2007; Deuschle et al., 2010). The role of 5-HTTLPR is discussed in more detail in Chapter 3.

1.2.4.2 GxE interactions

A number of studies have also identified the interplay between genes and environment to influence phenotype either in the form of gene-environment correlations (rGE) or gene-environments interactions. These are discussed in more detail in Chapter 3.

1.2.4.3 Environmental influences

The previous section, on heritability and genetic influences of sleep patterns, highlights that variability in sleep cannot be explained by *nature* alone. A number of *nurture* factors have been identified as determinants of variability in sleep phenotypes. Environmental influences of sleep often refer to parental expectations and practices with regards to infant sleep. These in turn are influenced by a multitude of factors, including the socio-cultural and environmental context, infant developmental history and age, individual sleep patterns, and parental personality and psychopathology. These factors have been incorporated into a model by Sadeh, Tikotzky and Scher (2010), which suggests that effects are bi-directional with both parental and infant related characteristics contributing to the maintenance of sleep problems in children. For example, the persistent link found between sleep problems and parental nocturnal involvement demonstrates this. A plausible explanation for this association is that infants who receive involvement during the nighttime may not develop self-soothing or regulating techniques since they rely on their parents to attend to them.

This section discusses some of these determinants in more detail, focusing on those which are of particular interest to this work (for a review of other environmental determinants see Lee & Rosen, 2012).

Breastfeeding

One such example is the case of breastfeeding. Newborns who are breastfed have been reported to show more fragmented sleep (Sadeh, Mindell, Luedtke, & Wiegand, 2009; Touchette et al., 2005), one study in particular reported that at 12 weeks of age infants who were breastfed were 8 times more likely to show delayed sleep consolidation (Simard, Lara-Carrasco, Paquette, & Nielsen, 2011). This has been attributed largely to the fact that breast milk is more easily digested therefore, newborns may require more feeding periods during the night (Sadeh, et al., 2010). As the infant develops, breastfeeding will no longer be needed to satisfy hunger, however, it is believed that it continues to act as a self-soothing technique (Sadeh, et al., 2010).

Maternal Cognitions

Maternal cognitions have also been identified as a strong predictor of infant sleep problems, particularly relating to difficulties with setting limits to parental nighttime involvement. Tikotzky et al. (2012) reported maternal cognitions to predict fragmented

sleep at 4 years of age. Earlier investigations reported similar findings. Maternal cognitions with regards to limit setting predicted active soothing and settling which in turn predicted number of nighttime awakenings (Morrell, 1999; Tikotzky & Sadeh, 2009). Maternal cognitions were also found to mediate the association between maternal postnatal depression and night waking (Teti & Crosby, 2012).

Couples Relationship

One of the few investigations to include paternal reports suggested that fathers' marital satisfaction and parenting stress and mothers' perceived social support predicted sleep and sleep changes at 2 years of age (Bernier, Bélanger, Bordeleau, & Carrier, 2012). This association was moderated by socioeconomic status (SES) such that this association did not hold statistically for families grouped in the high SES. However, in the low SES group lower levels of parenting stress and higher levels of social support reported by the father were associated with more consolidated sleep. Similarly for maternal reports in the low SES group, higher social support was associated with higher sleep consolidation.

Parental Psychopathology

Parental psychopathology has also been associated with sleep problems. Bi-directional effects are seen here as well, with parental mental health playing a major role in the processing of information with regards to child behaviour including sleep. However, disturbed infant sleep can act as a major stressor to family life thus affecting, parental mental health. Research on parental psychopathology has focused primarily on maternal depression. Mothers with postnatal depression have been found to report a higher frequency of infant sleep difficulties with findings ranging from the first weeks postpartum (Dennis & Ross, 2005; Karraker & Young, 2007; Murray, 1992; Stoléru, Nottelmann, Belmont, & Ronsaville, 2006). Contrary to these findings, some research suggests that although there is a small association between postnatal depression and infant sleep, once child variables and maternal sleep quality have been taken into account this association is diminished. A number of studies have also examined the extent to which infant sleep problems can impact on maternal well-being, particularly as they can be very disruptive to family life and cause sleep loss and feelings of fatigue (Piteo et al., 2012). Some of the contradictory findings may be due to methodological limitations of the studies and, as was discussed in the previous section, research on

infant sleep often has a wide ranging age group of children studied, timing of measurement and sampling of participants making it thus difficult to generalize the findings.

1.2.4.3.1 Infant Temperament

Temperament is a rubric in developmental psychology describing the stable individual differences in behaviour, reactivity and self-regulation, which are attributable to innate biological factors and which are influenced by experience and maturation (Rothbart & Bates, 2006; Schlotz & Phillips, 2009). Temperamental dimensions reflect behavioural tendencies rather than mapping directly onto discrete behavioural acts. Difficult temperament has been operationalized as a combination of intense emotional reactions, vigorous crying for longer periods, negative mood, poor adaptation to novel situations such as new people, foods or routines, and low regularity in biological rhythms. Infants with a difficult temperament may be at greater risk for emotional and behavioural problems (Guerin & Gottfried, 1994; Lee & Bates, 1985).

A number of studies suggest that there is an association between temperament dimensions and infant sleep and more specifically, it seems that sleep problems are over-represented in infants with difficult temperament (Carey, 1974; Ednick, et al., 2009; Halpern, Anders, Garcia Coll, & Hua, 1994; Keener, Zeanah, & Anders, 1988; Schaefer, 1990b; Scher, Tirosh, & Lavie, 1998; Spruyt et al., 2008; Weissbluth, 1983). Fussy, difficult temperament has also been shown to mediate the maintenance of sleep problems from the first to the second year of life by influencing the extent to which parents used physical comfort to help infants back to sleep.

This over-representation of difficult babies in groups of infants with sleep irregularities or disturbances does not seem surprising. One of the core aspects of temperament is the regularity of biological rhythms and this is often measured by assessing the regularity of feeding and sleeping patterns and behaviours. A number of studies have used recordings of sleep during the first days of life as indicators of regularity of biological rhythms to predict temperament (Carroll, Denenberg, & Thoman, 1999; Novosad, Freudigman, & Thoman, 1999). Only one study was identified which measured sleep and temperament and reported the two constructs to be independent of each other (Hayes, McCoy, Fukumizu, Wellman, & DiPietro, 2011). In a sample of 120, low risk,

healthy infants Hayes and colleagues measured sleep and irritable temperament at 6 weeks, 16 months and 24 months of age. Using Structural Equation Modelling the authors determined that although the constructs showed longitudinal stability they were independent of each other.

There are several methodological issues that make it difficult to disentangle the association between sleep and temperament.

A central methodological difficulty is the different assessment methods available for the measurement of temperament and sleep. There are several different methodologies available to measure temperament such as care-givers' reports, naturalistic observations and structured laboratory observations, the most common being parental reports and questionnaires (Damon, 1998). Similarly for sleep there are objective measures such as actigraphy and polysomnography and subjective measures such as parental reports (the methods for assessing sleep are discussed in more detail later in this chapter). Most studies have used maternal reports for both the assessment of sleep and temperament. The central methodological issue is that expectations about behaviour such as sleep and temperament have the potential to influence maternal perception and ratings. Given how intertwined the concepts of temperament and sleep are, behavioural patterns of one can influence the other. For example, Jimmerson (1991) studied 60 infants (30 with sleep problems and 30 without). The group of infants exhibiting sleep problems also had a higher proportion of infants with difficult temperament (26.6% vs. 6.6%) and were also more likely to be rated as having a 'more difficult than average' temperament rating (30% in infants with sleep problems vs. 0% in infants without), as reported by their mothers. Furthermore, a report by Scher et al. (1992). Using both maternal reports and actigraphy for the assessment of sleep revealed a higher number of correlations between sleep components and temperament when maternal reports were used compared to sleep components from actigraphy further indicating a rater bias. Additionally, studies have used a variety of developmental periods to assess temperament and sleep which cannot be readily compared to other developmental periods. Finally, the variety or often lack of information on other known determinants of infant sleep such as sleeping position, co-sleeping, exposure to maternal smoking, parental educational level, socio-economic status and mental health adds to the difficulty in understanding this association.

A more detailed description of the studies can be found in section 2.1.5.

1.2.5 Measurement of sleep

There are a number of ways of measuring sleep in children. Observations of an individual's sleep/wake cycle over a period of days or months can be measured via self or parental reports. Observations of the individual's sleep patterns, the various stages and characteristics of sleep can be measured by detecting electrical activity in the brain. Self-report of sleep, a widely used measure in adult studies, is often not an option when the participants are young children. Particularly in the study of infant sleep, recording and scoring techniques may influence results. For example, the timing and duration of the assessment can vary significantly between measures (e.g. laboratory vs. home environment, whole night vs. 24-hour recordings).

1.2.5.1 *Sleep questionnaires and diaries*

Sleep diaries are daily activity logs with a particular focus on activities preceding or succeeding sleep periods and have been found to provide reliable information on sleep-wake patterns (Monk et al., 1994; Rogers, Caruso, & Aldrich, 1993).

Questionnaires offer alternative measures of collecting information on sleep in a cost and time efficient manner. Sleep questionnaires collect information on a variety of sleep related behaviours and are most commonly used in large epidemiological studies.

Subjective reports of sleep, such as questionnaires, can document the subjective feelings and experiences of disturbed sleep which are often not documented through objective measures (Gregory & Sadeh, 2012). Furthermore, subjective measures of sleep are usually less costly and time-consuming and are thus more commonly found in large epidemiological studies, such as the study by Smaldone, Hong and Byrne (2009), which measured sleep in approximately 70,000 children.

Nevertheless, reporter bias is an important limitation of subjective reporting, for example in studies with parental report where parental characteristics such as mental health problems can impact the reporting of sleep or in the case where the same informant rates sleep and daytime functioning. There is also evidence that parents may not be aware of some of their children's sleep problems. For example, parents tend to overestimate their child's total sleep duration (Nixon et al., 2008). In addition, Owens, Spirito, McGuinn, & Nobile (2000) found that children self-identify more sleep problems than their parents.

1.2.5.2 Polysomnography

A common method regarded as the ‘gold standard’ to assess sleep, is polysomnography (PSG). PSG collects a variety of data:

- Electroencephalography (EEG) measures cortical activity by placing electrodes over certain areas of the brain.
- Electrooculography (EOG) measures the electrical activity of the muscles near the eye which indicates rapid-eye movement
- Electromyography (EMG) measures muscle activity by placing electrodes under the chin
- Electrocardiography (ECG) measures heart rhythms

Simultaneous recordings of these activities help to distinguish between the different stages of sleep (described earlier in section 1.2.1.2, page 29).

PSG is usually conducted in laboratory settings where the individual is monitored overnight. More recently, portable PSG devices have allowed data to be collected at home; however, in those circumstances controlling the setting and parameters of the environment is harder. PSG provides an accurate recording of the whole sleep period, allowing the researcher to distinguish between sleep stages and sleep disorders; however, recordings in the lab require the participant to spend the night in an unfamiliar, disruptive environment. Some portable PSG devices allow for the recordings to be conducted in the home; however, it is difficult to control conditions in such cases leading to variability between subjects. Furthermore, PSG records sleep during the night hours. When calculating sleep duration for young children who may have 1-2 naps daily, this could result in an underestimation of sleep duration by approximately 2 hours.

1.2.5.3 Actigraphy

An additional method for the objective recording of sleep is actigraphy. Actigraphy is currently the most reliable means of assessing an individual’s sleep/wake pattern against their rest/activity pattern. There are two applications of actigraphy; wrist and waist, of which wrist is the most common. In infants they have also been worn on the ankle. Wrist actigraphy measures rest/activity patterns through the use of a small device, similar to

a wristwatch. The actigraph, usually worn on the non-dominant wrist for adults and children and on the ankle for infants, collects information at regular time intervals determined by the researcher as the individual goes about their normal routine. The presence or absence of movement is used to determine the rest and activity periods.

Actigraphy is an objective, non-intrusive and non-supervised method that can be used for long-term recordings (e.g. days, weeks, months). The data is stored on the device and can be downloaded onto a computer once the recording has ended. Actigraphy is often used for the assessment of circadian rhythm disorders, which require long-term recordings, and has been found to correlate well with melatonin and temperature rhythms (Ancoli-Israel et al., 2003). Actigraphy is often used in conjunction with sleep diaries submitted by the individual being monitored, or in cases of young children by their parents.

Actigraphy is increasingly used in studies involving children with behavioural or neurological disorders. In the case of Attention-Deficit/Hyperactivity Disorder for example, where sleep disturbances are commonly reported by parents and children themselves actigraphy has been implemented to document such disturbances. Wiggs, Montgomery and Stores (2005) reported no differences in terms of sleep between ADHD subtypes and did not find sleep to predict ADHD severity.

A recent review by Meltzer et al. (2012) examined the use of actigraphy as a measure of sleep for paediatric research. The authors concluded that a lack of consistency exists in the reporting of methodological aspects of actigraphy and of actigraphy-measured variables. The authors further noted that there are only a small number of validation studies in the current literature, of which only 7 have compared actigraphy against PSG. The studies overall report a high sensitivity and low specificity and the authors concluded that actigraphy successfully identified sleep periods but less successfully identified wake periods after sleep onset. More specifically, Sadeh et al. (1991) reported an agreement rate of 85.3% between actigraphy and PSG, and concluded that actigraphy could accurately distinguish between sleep-disturbed and control children. However, Spruyt et al. (2010) found actigraphy to underestimate total sleep time and overestimate wake periods after sleep onset in a group of 149 school-aged children. A longitudinal analysis of actigraphy and PSG data from very young infants aged between 2 weeks and 6 months concluded that actigraphy was a valid measure of sleep in young infants compared to PSG (So, Buckley, Adamson, & Horne, 2005). In particular, the authors

reported an agreement rate of 93.7% at 2-4 weeks post birth and 91.6% at 5-6 months of age. The sensitivity values ranged between 91.2 – 96.2% during the first six months.

Van de Water et al. (2011) reviewed alternatives to polysomnography and concluded that different brands of actigraphs and algorithms can yield different agreement rates between PSG and actigraphy. The agreement rates depended on the population studied (e.g. normal vs. sleep disordered patients), the specific sleep variable of interest (for example sleep duration or wake after sleep onset), the manufacturer of the actigraphy device, and the algorithm and threshold used. There was an overall agreement rate of 72.1–96.5% between actigraphy and PSG (sensitivity range 86.5–98.7%, specificity range 27.7–67.1). The higher stability coefficients were found for recording of 14 consecutive days compared to 7 or 3 days (for examples, sleep duration 0.877, sleep efficiency % 0.922; compared with 7 days : 0.773, 0.839 (7 days) and 3 days: 0.479, 0.660). The authors conclude that actigraphy overall tends to overestimate sleep. Furthermore, movements during wakefulness were not always measured; as these periods were calculated as sleep resulting in less accurate estimates of sleep and wakefulness.

1.3 ANTENATAL DEPRESSION AND INFANT SLEEP

1.3.1 Animal research on antenatal stress and offspring sleep

The first studies to suggest that the antenatal environment may impact offspring sleep were conducted in animals. Rats stressed during fetal development exhibit higher levels of anxiety, greater vulnerability to drugs, and an increase in paradoxical sleep³. These effects, are believed to stem from permanent modifications to the functioning of the brain, more specifically to the feedback mechanism of the HPA axis. The dysfunction of the HPA is partly due to the increase of maternal glucocorticoids, which influence brain development. As a result, secretion of corticosterone is prolonged after stress and the number of central glucocorticoid receptors is reduced (Maccari et al., 2003). Antenatally stressed rats showed increased amounts of rapid eye movement sleep which positively correlated to plasma corticosterone levels (Dugovic, Maccari, Weibel, & Turek, 1999). Additional changes included increased sleep fragmentation, total light slow-wave sleep time and a slight decrease in the percentage of deep-slow wave sleep relative to total sleep time.

1.3.2 Research on antenatal depression and infant sleep in humans

There are very few studies which have examined the association between antenatal depression and infant sleep prospectively. This section describes in more detail these studies which can also be found in Table 1.

1. O'Connor and colleagues (2007) studied the effect of antenatal maternal mood on sleep disturbances in infancy and toddlerhood. Data from the Avon Longitudinal Study of Parents And Children (ALSPAC) were used. Maternal mood was measured antenatally at 18 and 32 weeks and postnatally at 8 weeks and 8 months using the Edinburgh Postnatal Depression Scale. Infant sleep was measured at 6, 18 and 30 months postpartum. Three aspects of infant sleep were assessed: a) total sleep time, b) nighttime awakening and c) sleep problems (referring to a broad phenotype of sleep patterns rather than specific problems). All data were collected via maternal reports and the sample size was n=10,323 mother-child dyads.

³ This is a stage of sleep, notable for a presence of REM, with high frequency brain activity in the forebrain and midbrain. It is characterized by dreaming and the inhibition of body movements, with the exception of the eye muscles and the diaphragm. It occurs cyclically several times during sleep, and the proportion of REM sleep changes dramatically during early infancy.

Information was also collected on alcohol consumption, smoking, educational level, crowding, birth weight and gestational age, maternal age and child sex. Parents who did not complete all the stages of the study were found to differ from participants: non-responders scored higher on anxiety and depression symptoms, reported higher tobacco use and lower birth weight, higher educational levels and maternal age. Maternal mood was not associated with infant total sleep time; however, there was a consistent link between maternal mood, number of nighttime awakenings and total sleep problems. Antenatal mood did not predict nighttime awakenings after controlling for postnatal mood; it did however continue to predict total sleep problems. Even though results are only based on questionnaire data the large sample size increases significantly the strength of the study.

2. Field and colleagues (2007) examined a more specific link between antenatal depression and infant sleep by examining maternal sleep disturbances which co-occurred with maternal depression during pregnancy. The study recruited 253 mothers, of which 85 met the criteria for depression at 32 weeks using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Mothers completed questionnaires on sleep disturbances, depression, anxiety and anger. Urine samples were also collected and analysed for cortisol and norepinephrine. The offspring's activity was measured both during pregnancy and postpartum. During pregnancy an independent rater observed the fetus for 5 consecutive minutes and recorded fetal activity every 3 seconds. Infants were observed for 15 minutes. Their rest-activity pattern was recorded every 10 seconds and categorized in one of 8 possible states according to Thoman's system of sleep recording⁴. Analysis revealed that during the second and third trimesters, depressed mothers reported more sleep disturbances and higher levels of anxiety, depression and anger. Furthermore, they had higher levels of cortisol and norepinephrine compared to controls. In particular, second-trimester maternal sleep disturbances correlated with depression and anxiety, norepinephrine levels and fetal movement, as well as with third-trimester sleep disturbances, levels of anxiety and anger, and cortisol levels. Newborns of depressed mothers were shown to spend less time in deep sleep and

⁴ a) Quiet sleep, b) active sleep, c) REM sleep, d) drowsy, e) inactive alert, f) active awake, g) crying, h) indeterminate sleep.

more time in indeterminate sleep or crying/fussy state compared to newborns of non-depressed mothers. In addition, newborns of depressed mothers were shown to be more active than infants of non-depressed mothers.

3. In a study by Diego and colleagues (2005), the differential effect of antenatal, postnatal and chronic depression on neonatal behaviour was examined. Mothers were recruited mid-pregnancy. Assessments took place during weeks 23-27 and again during the first two weeks post birth. The study recruited 20 mothers meeting criteria for each of the following categories: a) antenatal and postnatal depression, b) antenatal only, c) postnatal only, and d) non-depressed mothers, giving a total of 80 participants. Depressive symptoms were measured using the Centre for Epidemiological Studies-Depression scale (CES-D). The infant assessment consisted of two measures of behavioural observation. Firstly, the newborns' sleep/wake states were coded second by second for a period of 45 minutes. To categorize the infant's state the authors used Thoman's coding system, which was previously discussed in Field et al. (2007). Coders also indicated when infants exhibited the following behaviours: facial grimacing, yawning, sneezing, jerking, tremors and hiccups. Secondly, the Brazelton Neonatal Behaviour Assessment Scale (NBAS) was used to assess the infant's performance on habituation, orientation, motor behaviour, range of state, regulation of state, autonomic stability and abnormal reflexes. The NBAS also measured depression, excitability and withdrawal factors. Infants of mothers who were depressed both ante-and postpartum and infants of mothers depressed only during the antenatal period spent less time awake and alert and more time in a fussy/crying state. They also exhibited more activity and stress behaviours.
4. In a similar design, Field and colleagues assessed 140 1-day old infants and analysed a 3-hour recording of sleep. The authors reported that antenatal depression was associated with higher levels of indeterminate sleep (Field, Diego, Dieter, et al., 2004).
5. Similar results were reported by Jones and colleagues (Jones, et al., 1997). The authors measured sleep recordings of 44 infants at 1 month of age. The recordings were measured second by second. Infants of mothers with antenatal depression spent more time in indeterminate sleep, were less active and cried less. Mothers in

the ante- and postnatal depression group exhibited higher levels of depressive symptoms at both points compared to any other group. Analysis of the sleep/wake state observations revealed that infants of mothers depressed both ante- and postnatally and infants of mothers depressed antenatally only spent significantly less time awake and alert and more time in the fussy/crying state, compared to infants of non-depressed mothers. Infants whose mothers were in any of the depression groups spent more time in indeterminate sleep, compared to infants of non-depressed mothers. Greater activity and stress behaviour were shown by infants of mothers depressed at both time points (ante- and post-natal). Higher levels of stress behaviours were also exhibited by infants of mothers with antenatal depression only. The NBAS revealed that infants of mothers with depression during both the ante- and postnatal periods have lower habituation than infants of mothers with postnatal depression or controls. The study presents some interesting findings. Infants of mothers with depression at both time points seem to be at greater risk compared to other groups, with the infants performing worse on both the NBAS, especially the habituation scale, and the sleep/wake states. Given the strong evidence linking postnatal depression to adverse child outcomes, the lack of a significant difference on the NBAS between controls and the postnatal depression group might be explained by the early assessment time point, only two weeks post birth. Regarding infants of mothers with antenatal depression, they were significantly different to infants of non-depressed mothers in that they spent more time in the fussy/crying state and less time awake and alert. They also spent more time in indeterminate sleep. This might indicate that the timing of onset of depression might affect infant sleep differently.

6. Childhood sleep problems were also investigated in relation to well-being during pregnancy and current levels of maternal depression by Armstrong et al. (1998). Participants (n=47) consisted of a) mothers presenting children to a mother/baby hospital for alleviating sleep problems and b) matched controls. Information collected included socio-demographic data, pregnancy variables, maternal sleep

during pregnancy, and children's sleep characteristics and difficulties⁵. Maternal mood was measured with the EPDS in the postnatal period and a 12 item-scale for antenatal mood (developed for the purpose of this study). At the time of assessment the children were on average 12 months old. It is important to note here that the groups were compared based on children's sleep problems rather than maternal depression as in the previous studies. Cases were significantly different to controls in the following variables: length of daytime sleep, number of nighttime wakings on average and problem rating, with cases scoring higher on all the variables. Mothers of cases also scored higher on depressive symptoms at all time points (2nd and 3rd trimester and postnatally). While the study does report a link between maternal mood and child sleep problems at 1 year, findings should be interpreted with caution due to the limitations of the study. First, the questionnaires used were unstandardized and developed for the purpose of this study. Second, mothers were asked to complete questionnaires retrospectively: data may be biased since mothers were reporting on their mood more than 12 months after.

7. A more recent study by Armitage and colleagues (2009) examined the impact of maternal depression on early developmental changes in infant sleep. The sample consisted of 18 mothers and their infants. Maternal mood was used to categorize mothers in three groups and was measured using the SCID during the last trimester and the EPDS 2 weeks post birth. Three groups were formed consisting of 7 controls, 5 mothers with current major depressive disorder (MDD) and 6 mothers with either a history of MDD or a score of >10 on the EPDS. Infant sleep was measured using actigraphy for 7 consecutive days, starting 2 weeks postpartum and thereafter every month for six months. Participants were also asked to keep diaries of their infants' activities. Variables that were included as covariates were infant sex and maternal medication. Comparison of infant sleep in the groups of present MDD, past MDD or high level of depressive symptoms revealed no significant differences and so participants were combined to form one high-risk group (n=11). No differences were found in average sleep time between the high and low risk groups. However, differences were evident in the disruption of sleep measured as

⁵ Average length of daytime sleep, age at cessation of daytime sleep, time of night sleep, time taken to settle, method used to settle, current sleeping arrangements, average number of night awakenings.

nocturnal total sleep time, with low risk infants sleeping on average for 97 minutes longer. Differences were also evident in the number of sleep episodes, sleep efficiency and number of daytime sleep episodes. More disturbed sleep was found in the high-risk group where nocturnal sleep latency was longer, sleep episodes were shorter and sleep efficiency was lower as measured at 2 and 24 weeks post birth.

8. A large prospective questionnaire study was conducted by Nevarez and colleagues (2010) to examine early risk factors of sleep duration. Infants were assessed at 6 months, 1 year and 2 years of age. Maternal antenatal depression was assessed during the 2nd trimester using the EPDS. Information on infant sleep was collected through maternal reports at all 3 time points. Antenatal depression was associated with shorter sleep duration, with infants of antenatally depressed mothers sleeping on average 30 minutes fewer a day. Shorter sleep duration was also associated with the introduction of solid food before 4 months of age, childcare outside the home and TV/video viewing at years 1 and 2. Finally, the authors report differences in ethnic minorities who reported shorter sleep duration.

1.3.3 Summary of findings

The studies discussed all demonstrate an association between antenatal depression and disturbances in infant sleep. The different designs and measures used in the aforementioned studies to assess infant sleep and maternal depression make it difficult to draw firm conclusions.

Two studies used a combination of clinical diagnosis and screening questionnaires the remaining six used questionnaires. One study used actigraphy to measure sleep (Armitage et al., 2009), three used questionnaires and four used video recordings of infant sleep. Actigraphy and questionnaires have already been discussed as measures of assessing sleep earlier in this chapter and both have advantages and disadvantages. Observations of infant sleep via recording were not discussed and it is difficult to infer how representative observations are of the infants' daily sleep/wake state, since a maximum of 45 minutes is recorded. The samples also ranged significantly in sample size (n=18-10,323) and age of infants at assessment (1 day old – 30 months).

In conclusion, the studies would overall suggest an association between antenatal depression and infant sleep; infants of antenatally depressed mothers are at a higher risk for shorter sleep duration and more awakenings.

Table 1: Studies which have examined the association between antenatal maternal depression and child sleep.

Authors	Year	Country	Study design and number of participants	Age of children	Measure of depression	Measure of sleep	Results
O'Connor, T. G. et al	2007	UK	prospective longitudinal study, n=10,323	followed at 6, 18 and 30 months of age	EPDS	Questionnaires	Sleep problems at 18 and 30 months of age were associated with antenatal mood disturbance independent of postnatal mood. Awakenings were associated with antenatal mood but this association was not independent of postnatal mood.
Field, T., et al	2007	USA	prospective longitudinal study, n=253	neonates (1.3 days old on average)	SCID, Centre for Epidemiological Studies depression scale (CES-D)	15 minute sleep-wake observation measuring active sleep, quiet sleep, REM sleep, drowsy, active awake, crying, indeterminate sleep	newborns of depressed mothers spent less time in deep sleep, more time in indeterminate sleep and they were more active and fussy/crying
Diego, M. A., et al	2005	USA	prospective longitudinal study, n=80	1 week	(CES-D)	45minute observation measuring active sleep, quiet sleep, REM sleep, drowsy, active awake, crying, indeterminate sleep as well as facial grimacing, yawning sneezing, jerking, tremors and hiccups	Infants of mothers who were depressed both ante- and postpartum and infants of mothers depressed only during the antenatal period spent less time awake and alert and more time in a fussy/crying state. They also exhibited more activity and stress behaviours.

Authors	Year	Country	Study design and number of participants	Age of children	Measure of depression	Measure of sleep	Results
Field et al	2004	USA	Prospective longitudinal study, n=140	Day 1	CES-D	3 hour sleep recording measuring active sleep, quiet sleep, REM sleep, drowsy, active awake, crying, indeterminate sleep	antenatal depression symptoms was associated with higher levels of indeterminate sleep
Jones et al	1997	USA	Cross sectional observational study, n=44	1 month	CES-D & Diagnostic Interview Schedule for Children/Adolescents	Recording of sleep and second by second coding (time of recording not specified)	Infants of mothers with antenatal depression spent more time in indeterminate sleep, were active less and cried less
Armstrong	1998		Retrospective questionnaire study n=47	1 year of age	12 item scale developed for this study	questionnaire	Mothers with children with sleep problems scored higher on antenatal and postnatal depression scales
Armitage, R. et al	2009	USA	prospective longitudinal study, n=18	followed from 2 weeks to 6 months	SCID (classified as high risk if mother had current or history of MDD) Edinburgh Postnatal Depression Scale (EPDS) & Beck Depression Inventory (BDI-II) in the postpartum	Actigraphy	High risk group of infants took longer time to fall asleep, had more sleep bouts, lower sleep efficiencies and shorter nocturnal total sleep time compared to low risk infants.
Nevarez et al	2009	USA	Prospective longitudinal study, n=1676	6 months, 1 and 2 years of age	EPDS during 2 nd trimester of pregnancy	Maternal report of nighttime sleep duration and daytime naps at 6 months, sleep duration and daytime naps during 24 hour period at 1 and 2 years of age	Antenatal depression was associated with shorter sleep duration at all 3 time points, infants slept on average .36 fewer hours a day

1.4 RATIONALE & RESEARCH STRATEGY

One in ten women are affected by high levels of depression during pregnancy. There is substantial evidence suggesting that antenatal depression can affect fetal development. Children exposed to antenatal anxiety or depression are at higher risk of emotional and behavioural problems at 4 and 7 ½ years of age and antisocial behaviour at 16 years of age. More recently, antenatal depression has been associated with earlier markers of disturbed development including infant sleep, measured as shorter sleep duration, more nighttime awakenings and sleep problems.

This is important as sleep is a key predictor of development and disturbed sleep is a marker of neurodevelopmental disturbances, as well as being a significant source of stress to families. More specifically, there is evidence suggesting that shorter sleep duration negatively impacts on behaviour, cognitive and language development. Sleep problems during early life have been associated with later emotional and behavioural problems, language development and cognition. In very early life, when few reliable measures of healthy development exist, assessment of sleep provides a useful marker of child development, as well as a potential indicator for the emergence of problems later in life.

It is not yet fully understood what mechanisms are in play to confer this risk, although fetal programming effects of exposure to depression during pregnancy may be key. The early stages of life, including the fetal period, are characterized by rapid brain development, and sleep, as a marker of bio-behavioural organization, is an indicator of such neurodevelopment.

The association between antenatal depression and infant sleep has largely been established using parental reports of sleep and it remains to be determined whether this association holds when objective measures are used. Furthermore, it is unclear whether all infants are equally affected by maternal antenatal depression, an important consideration when targeting interventions. Finally, it is yet to be determined whether the association between antenatal depression and infant sleep is one of cause and effect.

1.5 AIMS AND STRUCTURE OF THE THESIS

This research aims to further our understanding of the association of antenatal depression with infant sleep in the following ways:

- a. By examining the role of two potential moderators i) infant reactivity and ii) the serotonin transporter promoter polymorphism 5-HTTLPR on the association between antenatal depression and infant sleep in two large cohorts the ALSPAC and Generation R studies in the UK and The Netherlands respectively (**Chapter 2 & 3**).
- b. By examining the association of antenatal depression with infant sleep in a pilot study using detailed behavioural and physiological measures, including objective measurement of rest/activity in mothers and their babies (**Chapter 4**).
- c. By examining infant sleep and temperament in children of women with antenatal depression who have undergone Cognitive Behavioural Therapy during pregnancy compared to a group of women without treatment using data from a pilot randomised controlled trial (ANTICIPATE trial). (**Chapter 5**)

Chapter 2: Antenatal depression and
infant sleep: The moderating effects
of infant reactivity: An investigation
in the ALSPAC and Generation R
cohorts

2 Chapter Overview

This chapter investigates the role of infant reactive temperament as a moderator of the association between antenatal depression and infant sleep. Identifying individuals who may be more susceptible to the effects of antenatal depression is crucial in, first, delineating the mechanisms through which depression impacts upon fetal and child development and, second, in designing and targeting interventions.

The analysis is conducted in two large population cohort studies: the Avon Longitudinal Study of Parents and Children (ALSPAC), based in the UK (n=8,991) and the Generation R cohort based in Rotterdam, The Netherlands (n=2,280). Data on infant sleep from the ALSPAC cohort were available at 3 time points (6, 18 and 30 months of age), and three aspects of sleep behaviour were examined: sleep duration, number of night awakenings and sleep problems. For Generation R, data were available at 6 and 24 months of age, while two aspects of sleep were available: sleep duration and number of night awakenings.

This is the first study to examine infant reactivity as a moderator of the association between antenatal depression and infant sleep. The chapter first describes two theories the diathesis-stress model and differential susceptibility theory and second, evidence to support the role of reactive temperament as a susceptibility factor. Some evidence is also presented for the association between sleep and reactive temperament. A description of the two cohorts follows. Hierarchical linear regression models were used to address the aims of the chapter. The chapter concludes with a discussion of the findings.

2.1 INTRODUCTION

A number of studies have established an association between antenatal maternal depression and infant development. Better understanding of whether some infants are more susceptible to environmental influences, including the intra-uterine environment, than others is needed in order to understand how antenatal depression impacts upon fetal and child development. The following sections discuss the theory of differential susceptibility (DST), a theoretical framework proposed to explain child development under adversity, which is an extension to a widely used theory, the diathesis-stress model, followed by a rationale for this study.

2.1.1 Diathesis-Stress Model

The diathesis-stress model is the dominant framework in developmental psychology used to interpret evidence of child development under adversity. The main premise of the model is that certain individuals may be more vulnerable to environmental stressors than others (Gottesman & Shields, 1967; Monroe & Simons, 1991; Zuckerman, 1999). This vulnerability may be genetic (e.g. the short alleles of the serotonin transporter promoter gene area 5-HTTLPR), behavioural (e.g. difficult temperament) or physiological (e.g. increased biological reactivity to stress) in nature. There is little evidence, however, as to whether these individuals are only disproportionately vulnerable or exclusively vulnerable to negative environmental influences compared to others. An inherent assumption of the diathesis-stress model is that individuals, although different in their vulnerability to negative environmental conditions, respond similarly to positive and supportive environmental conditions. Figure 3 depicts the predicted trajectories of individuals when placed in positive and negative environments. Individuals who are either resilient or vulnerable to negative environments perform similarly under positive environments, but have distinct developmental trajectories under stressful, adverse environments. Despite the wealth of evidence confirming that individuals do indeed differ in their vulnerability to adversity, there is limited empirical research supporting the hypothesis that they perform similarly under positive environments. A more recent theoretical framework, building on the diathesis-stress model, attempts to address this particular issue and provides an intriguing alternative possibility of differential susceptibility.

2.1.2 The theory of differential susceptibility (DST)

The theory of differential susceptibility (DST) was proposed by Belsky and colleagues (Belsky, 1997a, 1997b, 2005; Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007). The theory stipulates that certain individuals are more susceptible to both negative and positive environmental influences compared to others (malleable individuals). Malleable individuals are more receptive, more responsive and more adaptive to changes in their environment, whether these are negative or positive in nature (Figure 3 – plastic/malleable individual). They will do worse than average in negative environments but better than average in positive environments. In contrast a different group of individuals are less responsive to environmental input (shown in Figure 3 – fixed individual). It is anticipated that fixed individuals will follow a certain developmental trajectory with little influence from the environment, whether negative or positive. At the same time as the theory of differential susceptibility was formulated an independent yet similar theory was also proposed by Boyce and Ellis, known as the theory of biological sensitivity to context (Boyce & Ellis, 2005; Ellis & Boyce, 2008; Ellis, Essex, & Boyce, 2005). The two theories are broadly similar and share a large number of assumptions, primarily their focus on different developmental trajectories under positive environmental conditions (an analysis of where the two theories diverge can be found in Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011).

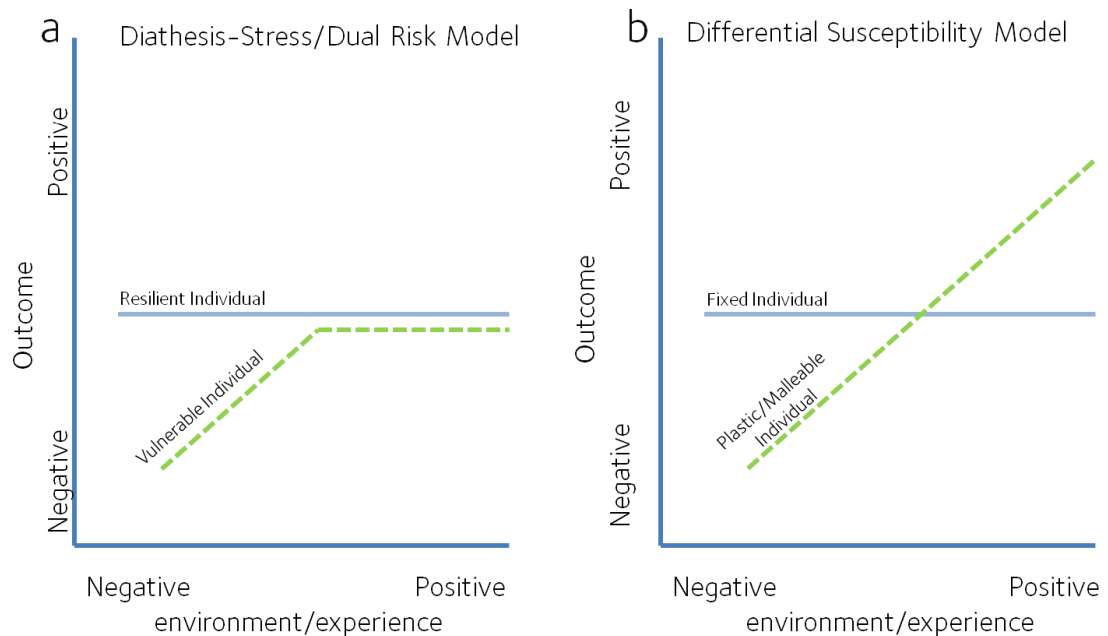


Figure 3: Illustration of a) diathesis-stress model (left) and b) differential susceptibility theory (right) (an adaptation from Bakermans-Kranenburg and Van IJzendoorn's (2007, pp. 1167, FIGURE 1).

The x and y axes represent the environment and outcome respectively ranging from negative to positive. The solid lines (parallel to the x axes) represent individuals less susceptible to environmental influences, whereas the dotted lines represent individuals more susceptible to environmental influences, also referred to as the “plastic” group. Plastic individuals when exposed to negative environments will be negatively affected whereas when placed to positive environments according to DST (graph B) will benefit the most.

2.1.2.1 Criteria For Establishing Differential Susceptibility

A number of criteria have been proposed by Belsky and colleagues (2007; 2009) to establish differential susceptibility. These are briefly summarized here and in Figure 4. Five criteria must be met. First, it is specified that the interaction effect has to be a cross-over interaction. Second, the susceptibility factor (also referred to as the moderator) and the predictor must be independent of each other. Third, the susceptibility factor and outcome must be independent. Fourth, the regression plot must be similar to the cross-over presented in Figure 3. Finally, the specificity of the model must be demonstrated by replacing the outcomes and susceptibility factors. Inherent to these criteria and Figure 3 are two assumptions: first, that the measurement of the environment covers a spectrum of negative to positive experiences; second, that the slopes of the susceptible group, as illustrated in Figure 3, are different from zero and steeper than the plot of the non-susceptible group.

-
1. **Statistical test for genuine (cross-over) interaction**
 2. **Test the independence of the susceptibility factor and the predictor**
 3. **Test of the association between the susceptibility factor and the outcome; if the association is nonzero, there is no support for differential susceptibility**
 4. **Comparison of the susceptibility regression plot with the prototypical graphical displays (as shown in Figure 3; only model b represents differential susceptibility).**
 5. **Test the specificity of the model by replacing susceptibility factors and outcomes**
-

Figure 4: Steps for testing differential susceptibility from Belsky, Bakermans-Kranenburg and Van IJzendoorn (2007, pp. 302, BOX 1).

2.1.3 Reactive temperament as a susceptibility factor

With the emergence of the theory of differential susceptibility Belsky (1997a, 1997b) also attempted to identify factors in developmental research that could act as markers of this susceptibility. A number of factors have been suggested as markers of susceptibility, which are now supported by empirical evidence at the genetic, endophenotypic and phenotypic levels. Examples of these include the serotonin transporter promoter gene (5-HTTLPR) and DRD4 at the genetic level (Bakermans-Kranenburg & Van IJzendoorn, 2006; Pluess et al., 2010; Taylor et al., 2006), blood pressure reactivity and cortisol reactivity at the endophenotypic level (Obradović, Bush, Stamperdahl, Adler, & Boyce, 2010) and difficult temperament at the phenotypic level (Belsky & Pluess, 2009; Kochanska, Aksan, & Joy, 2007; Lengua, 2008). Figure 3 illustrates how DST builds on and is different from the diathesis-stress model.

Reactive temperament has been operationalized as a combination of intense emotional reactions, vigorous crying for long periods, negative mood, poor adaptation to novel situations such as new people, foods or routines, and low regularity in biological rhythms. Temperamental characteristics are believed to reflect an individual's behavioural tendencies.

Belsky and Pluess (2009) discuss three potential explanations with regards to why reactive temperament can act as a marker of differential susceptibility. Firstly, Kochanska and colleagues (1993) have shown that more reactive infants have lower thresholds for anxiety and are thus more easily aroused by discipline and hence more

responsive to it. Secondly, Belsky (2005) argues that more reactive individuals have a more sensitive nervous system and thus environmental influences will register more strongly. Finally, Suomi (1997) draws on his work with rhesus macaques and argues that more fearful and inhibited macaques would spend more time observing other macaques in their environment and thus learn more than others about functioning efficiently in their environment. These observations put together would suggest the behavioural profile of a more vigilant and responsive organism.

A number of studies now empirically support reactive temperament as a susceptibility factor. To date no studies have used maternal mental health during the antenatal period as a marker of adversity, and so this section will discuss other studies which have used reactive temperament as a susceptibility factor. A recent review by Belsky and Pluess presented these studies. My searches identified three more, which were published since the review by Belsky and Pluess; these are presented in Table 2 (Belsky & Pluess, 2009; Morgan, Shaw, & Olino, 2012; Pitzer, Jennen-Steinmetz, Esser, Schmidt, & Laucht, 2011; Pluess & Belsky, 2010; Ursache, Blair, Stifter, & Voegtline, 2012).

A great level of heterogeneity was identified amongst these studies with regards to the definition of the susceptibility factor, the age of participants examined, the outcomes and environmental predictors investigated.

More specifically, 18 studies were identified which examined a spectrum of temperamental characteristics as a marker of differential susceptibility; including difficult temperament (for example Van Aken, Junger, Verhoeven, Van Aken, & Deković, 2007), fearfulness (Gilissen, Bakermans-Kranenburg, Van IJzendoorn, & Van Der Veer, 2008) and impulsivity (Lengua, 2008).

The age of children tested ranged from early infancy (6 months and 14-18 months old, Pluess & Belsky, 2010; Ursache, et al., 2012; Volling & Feagans, 1995) to late adolescence (17 years of age, Leve, Kim, & Pears, 2005).

Variability was found in terms of outcome examined with nine studies assessing externalizing behaviours (Bradley & Corwyn, 2008; Lengua, 2008; Leve, et al., 2005; Morgan, et al., 2012; Pitzer, et al., 2011; Pluess & Belsky, 2009, 2010; Smeekens, Riksen-Walraven, & van Bakel, 2007; Van Aken, et al., 2007) and others examining reading and social competence (Pluess & Belsky, 2010), depressive symptoms (Lengua,

2008) and attachment (Velderman, Bakermans-Kranenburg, Juffer, & van IJzendoorn, 2006). No studies were identified investigating sleep as an outcome.

Finally, great variability was also evident in environmental predictors used, which included harsh discipline (Leve, et al., 2005), maternal sensitivity (Bradley & Corwyn, 2008), parenting quality (Pluess & Belsky, 2010) and parental power assertion (Kochanska, et al., 2007). No studies using temperament as a susceptibility factor and maternal antenatal mental health, as exposure to an adverse environment, were identified.

The increasing number of studies, which examine child development under the framework of differential susceptibility, is encouraging in helping us understand who is most susceptible to environmental influences. The current evidence however, does not unequivocally support DST. There may be many explanations for this including, chance findings and small sample sizes. More importantly however, the studies do not all meet the criteria set out for establishing differential susceptibility, particularly, with respect to the predictor ranging from negative to positive and the moderator being independent from the predictor and outcome.

Table 2: Characteristics of studies reporting differential susceptibility using temperament as a susceptibility factor.

Study characteristics								Statistical differential	criteria susceptibility	for Follow-up analysis
Author	Year	Sample	Susceptibility: Plasticity Marker	Environmental Predictor	Range of Predictor	Outcome	Range of outcome	Moderator/ predictor correlation	Moderator/ outcome correlation	Subgroup contrasts
(Morgan, et al.)	2012	193 18-month boys/follow up at 5/6 years of age	Temperament: negative emotionality	Sibling relationship	A↔S	Internalizing Problems	N↔AN	ns	ns	means
(Pitzer, et al., 2011)	2011	308 boys and girls 8 years of age	Easy-difficult Self-control temperament	Parenting behaviour	A↔S	Behavioural problems	N↔AN	ns	Ns Sig for boys (easy temperament dimension only)	means
(Ursache, et al., 2012)	2012	1,293 48-month boys and girls	Negative reactivity	Infant regulation Parenting behaviour	A↔S	Executive function	P↔AN	significant	Not reported	means

Note: A: Adversity, S: Support/Enrichment, N: Negative outcome, AN: absence of negative outcome, P: positive, ns: non-significant

2.1.4 Antenatal depression and infant temperament

One complication of considering infant temperament, as a differential susceptibility factor in this context is that antenatal depression has been found to be associated with infant temperament, which, in theory, violates the second criteria for establishing DST. It is relevant, therefore, to discuss the evidence suggesting that antenatal depression predicts temperament and how this could fit in with the differential susceptibility theory.

Antenatal depression has been associated with reports of negative or reactive temperament, fussiness and crying as well as with higher levels of withdrawal, and less optimal performance on the neonatal behaviour assessment scale (Davis et al., 2007b; Field, 2011; Field, Diego, & Hernandez-Reif, 2006; Lundy et al., 1999a; McGrath, et al., 2008; Werner et al., 2007).

One plausible explanation is that this association could be due to shared genes between mother and child. An alternative hypothesis, in line with the idea of fetal programming, is that the fetus adapts to maternal cues about the outside world in an effort to achieve optimal functioning, and antenatal stress/depression could serve precisely as such a cue. Indeed, antenatal depression has been shown to predict several behavioural and physiological markers of differential susceptibility (Belsky et al., 2009; Belsky & Pluess, 2009). For example, other known susceptibility factors, such as the serotonin transporter gene 5-HTTLPR, may be interacting with environmental factors during fetal life to predict later development. Indeed one such investigation reports that infants exposed to antenatal depression and who were carriers of the short allele of 5-HTTLPR were more likely to score higher on reactive temperament at 6 months of age (Pluess, Velders, et al., 2010). This evidence would suggest that the antenatal environment has the potential to affect or guide one's plasticity to the environment⁶. A study by Pluess and Belsky (2011) provided similar evidence. Using the NICHD Study of Early Child and Youth Development, this study examined birth weight as a marker of adversity experienced during antenatal life. The authors report that lower birth weight did in fact predict greater infant difficulty. It is therefore not unreasonable to hypothesise that postnatal plasticity could be affected by prenatal programming. In fact Pluess and Belsky (2011) argue that developmental plasticity may also be a function of nurture.

⁶ Evidence on 5-HTTLPR however, is somewhat mixed as these findings were not confirmed in a large cohort study (Braithwaite et al, 2013).

There are a number of studies suggesting that this may be a plausible argument (Austin, Hadzi-Pavlovic, Leader, Saint, & Parker, 2005; Bergman, et al., 2007; Davis et al., 2005; Davis et al., 2004; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2002; Pesonen, Räikkönen, Strandberg, & Järvenpää, 2005). With this in mind, it is important to understand that these constructs of antenatal depression and infant temperament are interlinked and may indeed impact and guide a child's developmental trajectory.

In the present design, it was not possible to separate these constructs experimentally and this issue is therefore dealt with by statistical manipulation, discussed in more detail in the statistical analysis element of the methods section.

2.1.5 Infant sleep and reactive temperament

This section discusses the evidence for the association between infant sleep and temperament. This is essential in order to understand how the moderator, reactivity, and the outcome, infant sleep, are related. Statistical guidance for establishing moderation and criteria for establishing differential susceptibility both require the outcome to be independent from the moderator (also referred to here as susceptibility factor).

This question is particularly pertinent to this analysis, for two reasons. First, the definition of reactive temperament includes, as previously mentioned, regularity of biological rhythms, such as feeding or sleeping. Therefore, it is likely that there will be significant associations between those two measurements, as the measure of temperament often includes sleep as an indicator of regularity and predictability of rhythm. A common example of this would be ‘how easy the infant settles to sleep’. As a result, easy temperament is likely to include infants that settle to sleep well or easily. This brings us to the second reason, as this association between temperament (the moderator) and sleep (the outcome) is problematic particularly for establishing moderation. A few studies, which were also small in size, have addressed this question, most of which suffered from methodological limitations such as single informant bias.

Focusing on studies, which measured temperament within the first year of life, the literature search produces a small number of results. These studies are briefly discussed here, with more emphasis placed on studies which have measured reactive temperament and sleep characteristics such as those discussed in this chapter (sleep duration, awakenings, and sleep problems). Discussion is also extended to difficult temperament as the terms reactive and difficult are often used to describe similar temperamental characteristics.

Four studies were identified which used questionnaires as a mode of data collection. Carey (1974) measured temperament and sleep characteristics concurrently at 6 months and categorized infants (n=60) in those with and without night waking. A significant association was reported for infants with night-waking and low sensory threshold⁷, suggesting that infants more easily disturbed by sensory stimulation were also reported to have a higher number of night awakenings. Babies were categorised as having night

⁷ Sensory threshold is defined by the author as “the level of extrinsic stimulation that is necessary to evoke a discerning response”.

awakenings if they woke and cried at least once between 12am and 5am on at least 4 out of 7 nights a week for a minimum of 4 consecutive weeks between the age of 6 and 12 months. In a sample of 60 infants, Weissbluth (1983) reported that infants with difficult temperament slept less both during the day and night. The largest reported sample by Kelmanson (2000) (n=200), found that maternal reports of infant snoring or noisy breathing were associated with infant negative mood. Infants had been screened for other factors which may have influenced their breathing including allergies, family history of asthma, cranio-facial or upper airway abnormalities, hereditary respiratory diseases or protracted respiratory infections. Finally, Schaefer (1990a) examined infants with difficult temperament and found night time waking to be more prevalent in this group of infants compared to infants rated as having an easy temperament. The results held after controlling for gender, birth weight, gestational age, APGAR scores, mode of feeding, maternal age and smoking during pregnancy, amongst others. Infants' age in this study ranged from 6 to 36 months, which indicates that the observed temperamental characteristics may have varied significantly across infants, due to rapid developmental changes rather than due to individual differences in temperament.

Four further studies used more objective methods to assess sleep: Halpern and colleagues (1994) videotaped 21 full term infants at 3 weeks and 3 months of age to assess sleep. During these time points they also assessed temperament via maternal reports and conducted a behavioural assessment. Night awakenings at 3 weeks predicted maternal ratings of difficult and unpredictable temperament at 3 months of age. At this time, infants reported as having more night awakenings were also reported to be less approachable. Spruyt et al. (2008) used actigraphy to record the sleep of 20 infants monthly during the first year of life. Infants with 'easy' temperament⁸ were more likely to sleep longer.

Actigraphy was also used by Scher and colleagues (1998) with 30 12-month old infants to measure sleep duration, night awakenings, activity level, sleep efficiency and sleep onset time. Infants with higher scores on rhythmicity were going to bed earlier and had longer sleep duration but were also found to score lower on sleep efficiency measured as a percentage of total sleep time. No other temperamental categories were associated

⁸ Easy temperament here included the following scales: approachability, rhythmicity, adaptability and low distractibility

with infant sleep. Finally, Novosad and colleagues (1999), measured sleep during the first 2 days of life and found that sleep aspects significantly correlated with temperament measured at 8 months; however, different characteristics from the 1st and from the 2nd day were associated with temperament. It has been suggested that this might be related to release of stress hormones as a response to the birth process however this has not been empirically tested (Carroll, et al., 1999).

The evidence reviewed here suggests an association of disturbed sleep with difficult temperament, more specifically with temperamentally difficult infants exhibiting a higher number of night awakenings and shorter sleep duration.

2.1.6 Rationale

This chapter investigates the role of infant reactive temperament as a moderator of the association between antenatal depression and infant sleep. Identifying individuals who may be more susceptible to the effects of antenatal depression is crucial in, firstly, delineating the mechanisms through which depression impacts upon fetal and child development and, secondly, in designing and targeting interventions.

2.1.7 Aims & Hypotheses

The main aim of this chapter is to examine whether infants' reactive temperament acts as a moderator of the association between antenatal depression and infant sleep, using data from two large population cohort studies (ALSPAC and Generation R).

It is hypothesized that infants with highly reactive temperament will exhibit different sleep profiles when exposed to antenatal depression compared to those not exposed to antenatal depression. It is hypothesized that highly reactive infants in the context of antenatal depression will display

- i) shorter sleep duration
- ii) a higher number of night awakenings and
- iii) more sleep problems compared to less reactive infants.

2.2 STUDY I - THE AVON LONGITUDINAL STUDY OF PARENTS AND CHILDREN (ALSPAC)

2.2.1 Methods

2.2.1.1 *Setting and Procedure*

Mothers, their partners and their children participated in the Avon Longitudinal Study of Parents and Children (ALSPAC, Boyd et al., 2012). This is a longitudinal prospective study which included all pregnant women living in the area of Avon, England (the former county surrounding the city of Bristol), due to deliver between April 1st 1991 and December 31st 1992. 14,541 pregnant women were recruited, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. Questionnaires were sent to both parents at regular intervals during and after pregnancy. Informed consent was obtained from all participants and ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

2.2.1.2 *Participants*

In the current study, complete data was available for maternal depressive symptoms during pregnancy for 12,067 participants and sleep data were available for n=8,991 at 6 months of age. The attrition of participants at each stage is presented in Figure 5. Demographic characteristics of the sample used for this analysis were compared to characteristics of those with missing data (Table 3). Women for whom data was available for this analysis

- a. Were more likely to be married;
- b. Had higher educational qualifications;
- c. Lived with fewer people in the household;
- d. Were slightly older;
- e. Were more likely not to smoke;
- f. There were no differences in terms of infant gender and alcohol consumption;

Although many of the differences above were statistically significant, they were not very large in absolute magnitude (see Table 3).

There were differences between the remaining sample and the sample with missing data on the following sleep measures: 6 month awakenings⁹ and sleep problems at 18 months, where the included sample had slightly fewer awakenings at 6 months and more sleep problems at 18 months compared to the dropped-out sample. The samples were also different in sleep duration and awakenings at 30 months of age with the remaining sample sleeping less and waking up less compared to the dropped-out sample. There were no differences on any other sleep measures¹⁰. It was not possible to calculate differences for sleep problems at 30 months as there was no data from the missing data sample.

⁹ 6 month awakenings: mean=0.58 SE=0.01 vs. mean=0.51 SE=0.03 $t(11356)=-2.1$, $p=.036$, 18 month sleep problems: mean=2.1 SE=0.02 vs. mean=2.47 SE=0.05, $t(11033)=4.96$, $p<.001$, sleep duration 20 months: mean=12:44 SE=00:00 vs. mean=12:57 SE=00:03 $t(10003)=4.64$, $p<.001$ and sleep problems 30 month :mean=0.75 SE=0.01 vs. mean=0.94 SE=0.05 $t(10157)=3.52$, $p<.001$

¹⁰ Remaining vs. missing data sample: for sleep duration at 6 months mean=12:50, SE=00:01 vs. mean=12:49 SE=00:02, $t(10928)=-0.40$, $p=.69$, sleep duration at 18 months mean=11:19 SE=00:00 vs. mean=11:18 SE=00:01 $t(10876)=-0.86$, $p=.392$, sleep awakenings at 18 months mean=0.8 SE=0.01 vs. mean=0.85 SE=0.03 $t(10859)=$, $p=.072$

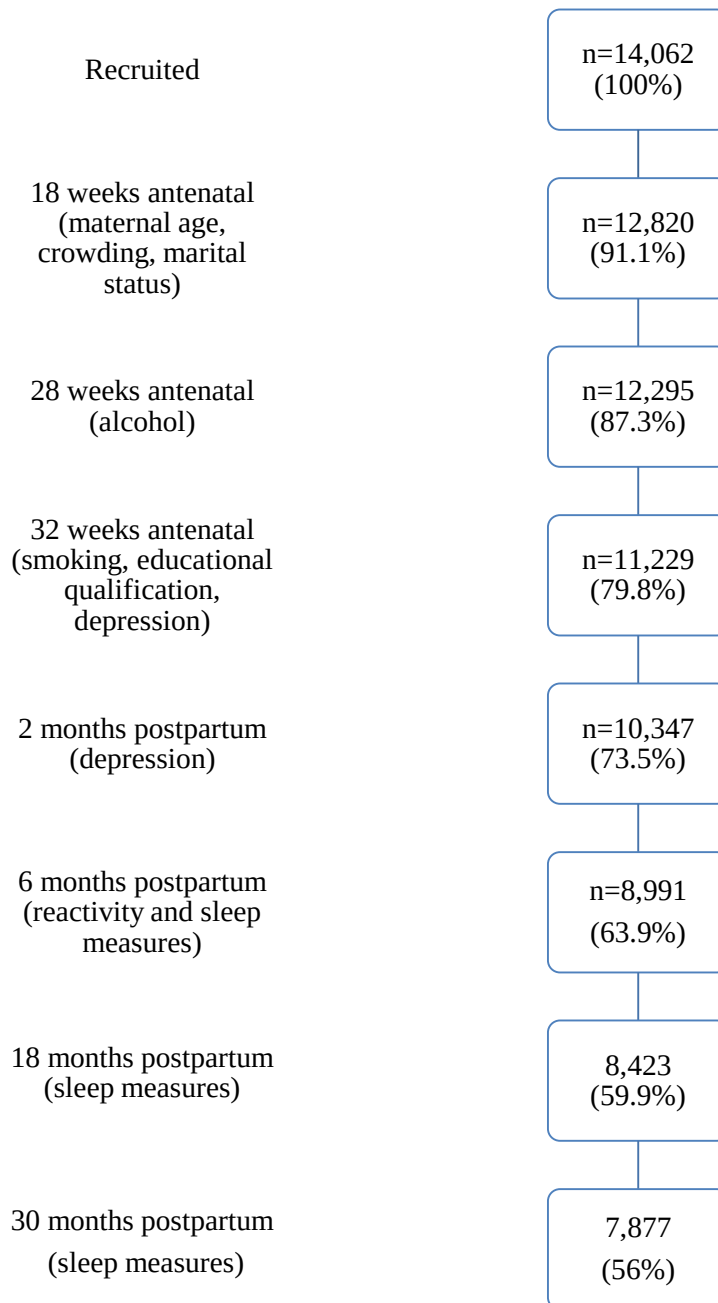


Figure 5: Diagram to represent attrition of data at each time point in the ALSPAC cohort.

Table 3: Comparison of demographic characteristics of the current sample (n=8,991) and the whole ALSPAC sample (n=14,062)

Variables	Sample for this Study (n=8,991)	Overall ALSPAC sample (N=14,062)	Test Statistic
<u>Maternal characteristics</u>	%	%	
Marital Status			
Never married	17	19.1	
Widowed	.1	.1	
Divorced	3.9	4.3	$\chi^2(5)=234.14, p<.001$
Separated	1.4	1.6	
1st marriage	70.7	68.4	
Marriage 2 or 3	6.9	6.5	
Educational Qualification			
CSE	13	20.2	
Vocational	9	9.8	$\chi^2(4)=427.1, p<.001$
O level	36.3	34.6	
A level	26	22.5	
Degree	15.7	12.9	
Smoking			
None	82.1	80.1	
1-9	7.1	7.7	$\chi^2(3)=189.07, p<.001$
10-19	8.1	9.1	
20+	2.7	3.2	
Alcohol (units per week)	mean=1.4, SD=3.24, range (0-70)	mean =1.67, SD=3.709, range (0-65)	t(4335)=-1.33, p=.185
Maternal age	mean =28.921, SD=4.48, range (15-44)	mean =28, SD=4.97, range (15-44)	t(4903)=-14.96, p<.001
Crowding	mean =1.58, SD=.61, range (1-4)	mean =1.67, SD=0.66, range(1-4)	t(4810)=13.71, p<.001
Ethnic Group			
White	98.6	97.4	$\chi^2(8)=91.56, p=.001$
Depression at 32 wks gestation	mean =6.71, SD=4.91, range (0-29)	mean =7.08, SD=5.08 range(0-29)	
<u>Child characteristics</u>			
Child Sex			
Male	51.8	51.7	$\chi^2(1)=0.95, p=.748$

2.2.1.3 Measures

2.2.1.3.1 Maternal Depression

The Edinburgh Postnatal Depression Scale (EPDS) was used to assess maternal depression at 32 weeks gestation and 8 weeks postpartum. The EPDS is a ten-item self-report scale developed by Cox, Holden and Sagovsky (1987) to measure mood disturbances in women during the perinatal period. The questionnaire asks participants to answer questions on their feelings in the past week. Scores on each question range from 0-3. A higher score on the scale indicates greater severity of depression. The scale has been validated for English speaking women in the antenatal and postnatal periods (Boyce, Stubbs, & Todd, 1993; Cox, Chapman, Murray, & Jones, 1995; Cox, et al., 1987; Harris, Huckle, Thomas, & Johns, 1989; Murray & Carothers, 1990; Murray & Cox, 1990). Using a cut-off score of 12/13 has yielded a specificity of 80-100% and a sensitivity of 80% for depressive disorder (Cox, Chapman, Murray, & Jones, 1996; Murray & Cox, 1990). In this sample α exceeded .80.

2.2.1.3.2 Infant reactivity

Infant temperament was assessed at 6 months using the Infant Temperament Questionnaire (Carey & McDevitt, 1978). This is a well-established and widely used questionnaire; examining nine domains of infant behaviour (activity, adaptability, approach, distractibility, intensity, mood, persistence, rhythmicity and threshold). 11 questions from the original questionnaire (out of 99 in total) were excluded from assessment in the ALSPAC study as piloting data indicated that more than 10% of the population did not respond to them. The items on the questionnaire consist of a 6-point scale ranging from “almost never” to “almost always” for parents to complete. Parents were asked “How often has the baby's recent behaviour been like the following descriptions”. The current study aimed to examine one temperamental aspect, that of reactivity. Three raters (Paul G. Ramchandani, Marinus van IJzendoorn and Marian Bakermans-Kranenburg) examined all the items on the questionnaire independently and identified the items which pertained to the concept of reactivity (Ramchandani et al., 2010). These corresponded to the items in the following scales from the Infant Temperament Questionnaire: intensity, threshold, approach, adaptability (40 items in total). Individual item scores were summed to form a reactivity scale. Cronbach's α = .75

indicated good internal reliability. This was the earliest measure of temperament available and took place before the assessment of most sleep measures.

2.2.1.3.3 Infant Sleep

Infant sleep was assessed by maternal report at 6, 18 and 30 months. Parents were asked to report the number of hours their children slept during a typical night and day period and the number of awakenings during the night (for example “On a normal day what time in the evening does your baby go to sleep?”). Sleep problems were additionally assessed at 18 and 30 months by asking parents to report on items such as whether the child regularly refuses to go to bed, wakes very early, has difficulty going to sleep, has nightmares or wakes in the night. These were recorded as a yes/no response and a sum score of these 7 items was used. Reliability analysis indicated good alphas at both time points ($\alpha=.71$ for 18 months, and $\alpha=.72$ for 30 months).

2.2.1.3.4 Covariates

A number of variables were included as covariates to control for possible confounding effects. Key variables were identified and added to the analysis according to recommendations by Weinberg (1993) and based on whether

- i. they were associated with the outcome or predictor variables
- ii. there was empirical evidence to suggest they may act as confounders

The following variables were included: marital status, crowding, maternal age, (assessed at 18 weeks gestation) and maternal smoking; alcohol consumption at 28 weeks and educational qualification (at 32 weeks gestation). Postnatal depression assessed at 2 months postpartum was also included.

2.2.1.4 Analysis Plan

The key analysis was designed to test whether reactivity moderated the association between antenatal depression and infant sleep at three time points: 6, 18 and 30 months of age. The analysis was undertaken in a series of stages.

First, descriptives for antenatal depression, infant reactivity and sleep measures were examined. Any differences in sleep by gender were tested for using independent t-tests.

Second, associations of sleep items with depression, reactivity and covariates were analysed using Pearson (two-tailed) correlations. Due to the large number of correlations undertaken, a conservative approach was adopted and Bonferroni correction for multiple testing was applied where possible. In some cases, such as section 2.2.2.3, there were 72 planned correlations resulting in a $p=\alpha/n$ of correlations $=.05/72=.00069$. In these instances values of $p=.001$ and below were accepted.

Third, the aim of the chapter was addressed using hierarchical linear regressions. In the first step of the regression analysis all the covariates including gender were added. Gender was added to the model due to evidence that boys and girls are affected differently following exposure to parental depression (Murray, 1992). In the second step the predictor variable, antenatal depression and moderator variable, infant reactivity, were added and in the third step three 2-way interactions, between the predictor and moderator were introduced (depression x reactivity, depression x gender, gender x reactivity). Finally, in Step 4 a 3-way interaction term was introduced: depression x reactivity x gender. Figure 6 schematically presents the 4 steps of the regression models. Due to the more limited number of regression analyses examined here and the exploratory nature of the analysis, Bonferroni correction was not applied.

In accordance with recommendations by Aiken and West all variables were centred on zero prior to entering them in the regression to avoid issues of multi-collinearity (Aiken, West, & Reno, 1991). Following criteria to establish moderation based on the McArthur approach (Kraemer, 2008) the moderator (reactivity) has to be independent of the outcome (sleep) and the predictor (antenatal depression). In cases where neither of the two criteria were met, reactivity was regressed on sleep first and on antenatal depression second. The regression analyses were then re-run using the residuals for sleep and depression in the model. Using the residual terms did not change the results. The

regression models with the residual terms are presented here. Where a significant interaction emerged, this was further explored, by repeating the regression for boys and girls separately and by exploring the interaction graphically. All statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) version 20.0 (IBM, 2011).

Dealing with Missing Data

In this cohort missing data and selective attrition resulted in significant data loss, an important issue with longitudinal cohorts that needs to be addressed and which may affect the results described in the next section. Options for dealing with missing data were carefully considered prior to the analysis and imputation was identified as a useful technique used for this purpose. The following points discuss why this option was not utilised.

It is recommended that imputation is used to address missing data in confounders rather than in the main predictor and outcome variables as it may affect the results in unpredictable ways. In this cohort 30% of the data ($n=4,194$) was missing either due to the main predictor or the moderator.

Previous imputation models using the ALSPAC cohort suggest that imputing the confounder does not alter the fundamental association but rather may affect the confidence intervals (Ramchandani et al., 2008).

Finally as this was a cross cohort analysis the variables between cohorts were not identical and it was decided that imputation of the counfounders may also have affected the results in unpredictable ways.

Due to the aforementioned reasons and as these are labour intensive techniques it was decided that missing data would not be addressed for this analysis.

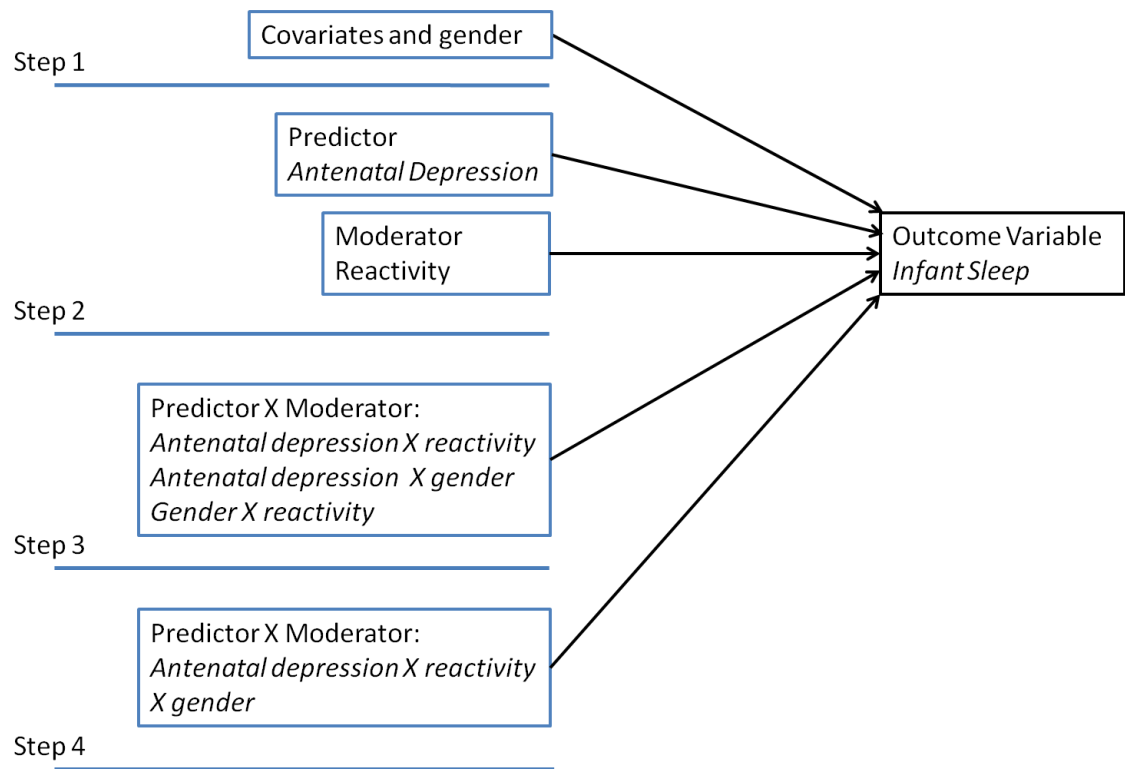


Figure 6: Schematic diagram of moderator analysis

2.2.2 Results

2.2.2.1 Treating the Data

Tests of normality were conducted for all measures. Measures of sleep, antenatal depression and reactivity were not normally distributed. Transformation of the data was attempted (using Log and Square root transformations); however, distributions were not normalised. With large datasets, such as this one, both the Kolmogorov-Smirnov and Shapiro-Wilk test may give a significant p value even with small deviations from normality (Field 2009); for that reason histogram plots were examined. Outliers ($z > |3.29|$) were Winsorised by replacing the outlying score with the next highest value (with $z < |3.29|$)¹¹.

2.2.2.2 Descriptive Statistics

Antenatal depression and reactivity data were available for $n=9,868$ participants¹². As expected the average score for depression was low ($M=6.73$) but participants' scores ranged from 0 to 29. Table 4 presents the descriptives for antenatal depression and reactivity.

Table 4: Descriptives for antenatal depression at 32 weeks gestation and reactivity 6 months postpartum ($n=9,868$)

	Mean	SD	Range	Median
Antenatal depression	6.73	4.91	0-29	6.00
Reactivity	81.48	16.23	16-163	82

¹¹ The following number of values were Winsorised for each variable: 6 month sleep duration ($n=59$), awakenings ($n=120$), 18 month sleep duration ($n=39$), awakenings ($n=81$), sleep problems ($n=0$), 30 month sleep duration ($n=7$), awakenings ($n=4$), sleep problems ($n=0$), antenatal depression ($n=25$) and reactivity ($n=25$).

¹² A Kolmogorov-Smirnov test was performed and the data were found to be non-normally distributed, $D(9868) = .116$, $p < .001$ for antenatal depression and $D(9868) = .024$, $p < .001$ for reactivity.

Descriptive characteristics for total sleep time, number of awakenings and sleep problems are presented in Table 5¹³. Descriptives for all sleep variables are also presented by gender.

At 6 months of age, boys slept less on average compared to girls ($M=12:44$, $SE=00:03$ vs. $M=12:58$, $SE=00:03$, $t(8626)=-5.82$, $p<.001$) and had a higher number of awakenings ($M=.67$, $SE=0.02$ vs. and $M=.45$, $SE=0.02$, $t(8155)=7.5$, $p<.001$).

At 18 months of age boys slept slightly less on average than girls ($M=11:17$, $SE=00:00$ vs. $M=11:24$ $SE=00:01$, $t(8005)=5.05$, $p<.001$). There were no significant differences in number of night awakenings and sleep problems at this age between boys and girls ($M=.81$, $SE=.017$ vs. $M=.76$, $SE=.017$, $t(8000)=1.9$, $p=.056$. and $M=2.2$, $SE=0.03$ vs. $M=2.15$, $SE=0.03$, $t(8101)=1.4$, $p=.162$ respectively).

At 30 months of age where boys slept slightly longer than girls ($M=12:48$ $SE=00:00$ vs. $M=12:39$, $SE=00:00$, $t(7527)=6.79$, $p<.001$) but there were no gender differences in number of night awakenings and sleep problems ($M=.75$, $SE=.016$ vs. $M=.73$, $SE=.018$, $t(7580)=1.09$, $p=.277$ and $M=3.08$, $SE=.032$ vs. $M=3.04$, $SE=.033$, $t(7377)=.97$, $p=.334$ respectively).

¹³ A Kolmogorov-Smirnov test was performed and the data were found to be non-normally distributed at **6 months** for total sleep time $D(9506)=.105$, $p<.001$ and number of awakenings per night $D(9506)=.439$, $p<.001$; at **18 months** for total sleep time $D(9506)=.160$, $p<.001$, number of awakenings per night $D(9506)=.135$, $p<.001$ total sleep problems $D(9506)=.275$, $p<.001$; and at **30 months** for total sleep time $D(9873)=.117$, $p<.001$, number of awakenings per night $D(9873)=.140$, $p<.001$, total sleep problems $D(9873)=.135$, $p<.001$.

Table 5: Descriptives for total sleep time, awakenings and sleep problems in the ALSPAC cohort

6 months of age			18 months of age			30 months of age			
Total sleep time (hh:min)									
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
Mean	12:44	12:58	12:50	11:17	11:24	11:20	12:48	12:39	12:44
SD	01:58	01:53	01:59	00:59	01:00	01:00	00:57	00:56	00:57
Range	06:00-19:30	06:00-19:00	06:00-19:30	08:00-14:30	08:00-14:30	08:00-14:45	09:30-16:00	9:30-16:00	09:30-14:00
Night awakenings									
Mean	.67	.45	.53	.81	.76	.79	.73	.72	.75
SD	1.5	1.11	1.14	1.08	1.07	1.09	.98	1.01	1.07
Range	0-4	0-12	0-12	1-11	0-11	0-11	0-13	0-15	0-15
Median	2	2	2	0	0	0	0	0	1
Sleep Problems									
Mean				2.23	2.15	2.19	3.06	3.02	3.07
SD				1.89	1.91	1.9	1.97	1.98	1.98
Range				0-7	0-7	0-7	0-7	0-7	0-7
Median				2	2	2	3	3	3
n	4886	4620	9506	4359	4143	8502	3741	3507	7248

2.2.2.3 *Correlational analyses of sleep variables*

Correlational analyses were conducted to explore the bivariate associations between sleep variables at all 3 time points¹⁴. Data presented in Table 6 indicated that all variables were correlated to each other showing aspects of stability and continuity in the assessment of sleep across time.

Correlations of total sleep time at 6 months with total sleep time at 18 and 30 months revealed a negative association ($r = -.338$, $p < .001$ for sleep duration at 6 and 18 months, and $r = -.258$, $p < .001$ for sleep duration at 6 and 30 months). Awakenings at different time points were all positively associated, with coefficients ranging from low ($r = .173$, $p < .001$ for awakenings at 6 months and 30 months) to moderate ($r = .455$, $p < .001$ for awakenings at 18 and 30 months). Sleep problems at 18 months were significantly correlated to sleep problems at 30 months ($r = .452$, $p < .001$).

Correlations for depression, sleep variables, reactivity and socio-demographic characteristics were examined and are presented in Table 7¹⁵. Antenatal depression was not associated with sleep duration at any 3 time points but was associated with number of night awakenings and sleep problems. It is interesting to note that reactivity was correlated to all sleep variables with coefficients of small magnitude.

¹⁴ Bonferroni correction $p = \alpha / n$ of correlations = $.05 / 29 = .0017 = .002$.

¹⁵ Bonferroni correction $p = \alpha / n$ of correlations = $.05 / 72 = .00069 = .001$.

Table 6: Unadjusted associations for sleep variables at 6, 18 and 30 months of age (n=8,052)

		6 months		18 months			30 months		
		Total sleep time	Number of awakenings	Total sleep time	Number of awakenings	Sleep problems	Total sleep time	Number of awakenings	Sleep problems
6 months	Total sleep time	_____	-.254**	-.338**	-.218**	-.243**	-.258**	-.168**	-.160**
	Number of awakenings		_____	.126**	.260**	.169**	.093**	.173**	.088**
18 months	Total sleep time			_____	.257**	.300**	.552**	.183**	.177**
	Number of awakenings				_____	.443**	.185**	.455**	.263**
	Sleep problems					_____	.197**	.291**	.452**
30 months	Total sleep time						_____	.214**	.363**
	Number of awakenings							_____	.240**
	Sleep problems								_____

** . Correlations significant at the .001 level

Table 7: Unadjusted associations between sleep variables, reactivity, depression scores and covariates at 6, 18 and 30 months of age (n=8,007)

		6 months		18 months			30 months		
		Total sleep time	Awakenings per night	Total sleep time	Awakenings per night	Sleep Problems	Total sleep time	Awakenings per night	Sleep Problems
Moderator	Reactivity	-.126**(.000)	.095**(.000)	.077**(.000)	.119**(.000)	.163**(.000)	.055**(.000)	.090**(.000)	.136**(.000)
	Antenatal	-.018(.102)	.031(.005)	.024(.030)	.071**(.000)	.155**(.000)	.012(.286)	.057**(.000)	.179**(.000)
Depression Scores	Postnatal	-.052**(.000)	.029(.006)	.039**(.000)	.092**(.000)	.145**(.000)	.034(.003)	.052**(.000)	.164**(.000)
	Crowding	.024(.028)	.011(.293)	.012(.268)	.053**(.000)	.068**(.000)	-.028(.014)	.015(.203)	.041**(.000)
Covariates	Ed Qual.	.002(.872)	.083**(.000)	-.006(.622)	.069**(.000)	.141**(.000)	.021(.064)	.051**(.000)	-.117**(.000)
	Smoking	.020(.058)	.041**(.000)	-.050**(.000)	.009(.419)	.066**(.000)	-.030(.010)	.002(.841)	.087**(.000)
	Marital status	.028(.008)	.002(.867)	.006(.583)	-.019(.091)	.084**(.000)	.006(.608)	-.014(.233)	-.081**(.000)
	Alcohol	-.008(.475)	.007(.521)	.000(.990)	.000(.995)	.033(.003)	.039*(.001)	.005(.678)	.039*(.001)
	Maternal Age	-.044**(.000)	.070**(.000)	.110**(.000)	.015(.181)	.106**(.000)	.125**(.000)	.014(.225)	-.107**(.000)

*. Correlations significant at the .001 level, **. Correlation is significant p< 0.001 level (2-tailed).

2.2.2.4 Moderator analysis

2.2.2.4.1 Sleep at 6 months of age: Does reactivity moderate the association between antenatal depression and infant sleep at 6 months of age (total sleep time and awakenings)?

Two hierarchical linear regressions were conducted to assess whether reactivity moderated the association between antenatal depression and a) total sleep time and b) awakenings at 6 months of age. The results of this analysis are presented in Table 8 and Table 9. Data on sleep problems at 6 months of age were not available.

Total Sleep Time

In Step 3, the depression x reactivity interaction term emerged as significant ($\beta = -.043$, $p < .001$) and there was weak evidence for reactivity x gender ($\beta = .064$, $p = .057$).

The 3-way-interaction term was added in step 4 but was not found to be significant ($\beta = .008$, $p = .810$).

Table 8: Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and total sleep time at 6 months (n=8,678)

Variables	Step 1 R ² =.012					Step 2 R ² =.012					Step 3 R ² =.015					Step 4 R ² =.015				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Step 1																				
Postnatal Depression	-.008	.002	-.036	-3.358	.001	-.010	.003	-.049	-3.745	.000	-.010	.003	-.048	-3.683	.000	-.010	.003	-.048	-3.688	.000
Gender	.135	.021	.069	6.458	.000	.135	.021	.069	6.453	.000	.134	.021	.068	6.406	.000	.134	.021	.068	6.405	.000
Ed. Qualification	.016	.009	.020	1.693	.091	.016	.009	.021	1.787	.074	.016	.009	.021	1.786	.074	.016	.009	.021	1.787	.074
Alcohol	-1.597	.003	.000	-.005	.996	.000	.003	-.001	-.071	.943	.000	.003	-.001	-.093	.926	.000	.003	-.001	-.091	.928
Smoking	.039	.016	.028	2.484	.013	.038	.016	.027	2.397	.017	.037	.016	.026	2.343	.019	.037	.016	.026	2.338	.019
Crowding	.054	.018	.034	3.016	.003	.051	.018	.032	2.873	.004	.051	.018	.032	2.835	.005	.050	.018	.032	2.826	.005
Marital Status	.033	.008	.050	4.399	.000	.034	.008	.051	4.489	.000	.034	.008	.051	4.475	.000	.034	.008	.051	4.477	.000
Maternal Age	-.013	.002	-.060	-5.183	.000	-.013	.002	-.060	-5.147	.000	-.013	.002	-.060	-5.170	.000	-.013	.002	-.060	-5.172	.000
Step 2																				
Antenatal Depression						.023	.013	.023	1.752	.080	.044	.034	.045	1.294	.196	.044	.034	.045	1.302	.193
Reactivity						.003	.011	.003	.237	.813	-.059	.033	-.060	-1.772	.076	-.059	.033	-.060	-1.776	.076
Step 3																				
Depression x Gender											-.013	.021	-.021	-.637	.524	-.014	.021	-.022	-.645	.519
Depression x Reactivity											-.042	.011	-.043	-3.980	.000	-.050	.033	-.050	-1.490	.136
Reactivity x gender											.040	.021	.064	1.904	.057	.040	.021	.065	1.911	.056
Step 4																				
Depression x Reactivity x Gender																.005	.021	.008	.240	.810
	F(8,8678)=13.177,p<.001					F(10,8676)=10.85,p<.001					F(13,8673)=9.934,p<.001					F(14,8672)=9.228,p<.001				

Awakenings

This model followed an identical structure to the one previously described for sleep duration at 6 months. A summary of the results is presented here (only Step 4). The whole regression model can be found in the Appendices (Appendix 2 page 281). There was no evidence to suggest that reactivity and gender moderated the association between antenatal depression and infant sleep ($\beta = -.013$, $p = .694$).

Table 9: Summary of Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on the association between antenatal depression and number of awakenings at 6 months, Step 4 (n=8,909)

Variables	Step 4 R ² =.025	
	β	p
Step 1		
Postnatal Depression	.006	.643
Gender	-.088	.000
Ed. Qualification	.076	.000
Alcohol	.000	.983
Smoking	-.044	.000
Crowding	.033	.003
Marital Status	-.030	.007
Maternal Age	.073	.000
Step 2		
Antenatal Depression	.010	.760
Reactivity	.062	.063
Step 3		
Depression X Reactivity	.017	.599
Depression X Gender	.017	.599
Reactivity X Gender	-.052	.116
Step 4		
Depression X Reactivity X Gender	-.013	.694
F(14,8894)=16.032, p<.001		

2.2.2.4.2 Sleep at 18 months of age: Does reactivity moderate the association between antenatal depression and infant sleep at 18 months of age (total sleep time, awakenings and sleep problems)?

Three hierarchical linear regressions were calculated to examine whether reactivity and gender moderated the association between antenatal depression and total sleep time, awakenings and sleep problems at 18 months of age. A summary of the results are presented here (Table 10). The full regression models can be found in the Appendices (Appendix 3, Appendix 4 and Appendix 5).

Total Sleep Time

There was no evidence that infant reactivity and gender moderated the association between antenatal depression and infant sleep at 18 months of age ($\beta = -.014$, $p = .688$).

Awakenings

There was however, evidence to suggest that the association between antenatal depression and infant night awakenings was moderated at 18 months of age by reactivity and gender ($\beta = -.085$, $p = .013$). This interaction was further explored by repeating the regression models by gender, which revealed that the interaction depression X reactivity was significant for boys ($\beta = .047$, $p = .002$) but not for girls ($\beta = -.007$, $p = .676$).

Sleep Problems

A significant 3-way interaction was also found for sleep problems ($\beta = -.089$, $p = .008$). Further analysis revealed a similar pattern by gender where the interaction term depression X reactivity was only found to be significant for boys ($\beta = .059$, $p < .001$) but not for girls ($\beta = .003$, $p = .834$).

The interactions for night awakenings and sleep problems were also explored graphically to illustrate the direction of these effects (Figure 7). Both graphs illustrate that reactive vs. non-reactive boys scored similarly when their mothers had not been depressed; however, in the case of infants whose mothers had experienced antenatal depression, highly reactive boys exhibited a higher number of awakenings and sleep problems compared to the low reactivity group. The separate groups are joined by straight lines only for illustrative purposes, despite being independent, to demonstrate whether the criterion regarding crossover as laid out in Figure 4, on page 64 was met.

Table 10 : Summary of Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and a) sleep duration, b) number of night awakenings and c) sleep problems at 18 months, Step 4.

Variables	Total sleep Time		Awakenings		Sleep Problems	
	Step 4 R ² =.021		Step 4 R ² =.014		Step 4 R ² =.042	
	β	p	β	p	β	p
Step 1						
Postnatal Depression	.027	.044	.066	.000	.072	.000
Gender	-.055	.000	-.022	.046	.076	.006
Ed. Qualification	-.045	.000	-.079	.000	-.171	.000
Alcohol	-.010	.370	-.006	.606	.032	.003
Smoking	-.059	.000	-.030	.009	.019	.087
Crowding	-.005	.665	.034	.003	.024	.029
Marital Status	-.029	.011	-.017	.131	.049	.085
Maternal Age	.127	.000	.048	.000	-.084	.000
Step 2						
Antenatal Depression	.024	.495	-.022	.522	.024	.486
Reactivity	.056	.107	-.032	.360	.006	.851
Step 3						
Depression x Gender	.035	.300	.032	.356	.056	.093
Depression x Reactivity	.000	.997	.101	.003	.116	.001
Reactivity x Gender	-.051	.062	.021	.540	-.025	.453
Step 4						
Depression x Reactivity x Gender	.014	.688	-.085	.013	-.089	.008
	F(14,8303)=13.129, p<.001 N=8,318		F(14,8295)=9.546, p<.001 N=8,310		F(14,7657)=31.130, p<.001 N=8,423	

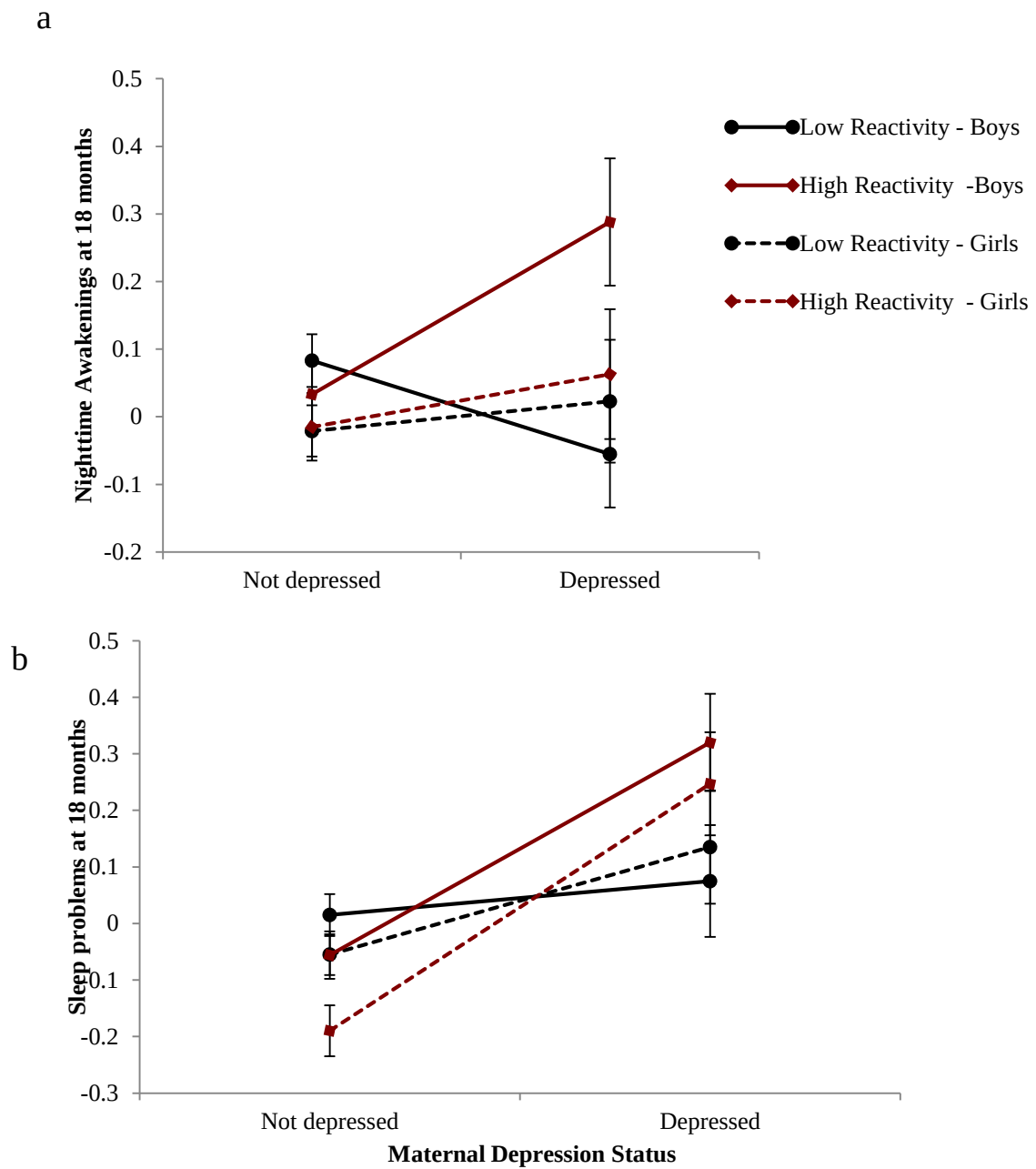


Figure 7: Association between antenatal depression and infant sleep a) night awakenings and b) sleep problems in boys and girls, moderated by reactivity, using standardized residual scores, EPDS cut-off used >12 for Depressed vs. Not depressed.

2.2.2.5 Sleep at 30 months of age: Does reactivity moderate the association between antenatal depression and infant sleep at 30 months of age (total sleep time, awakenings and sleep problems)?

Three hierarchical linear regressions were conducted to assess whether reactivity and gender would moderate the association between antenatal depression and a) total sleep time, b) awakenings and c) sleep problems at 30 months of age.

Total Sleep time

There was no evidence of a moderating effect ($\beta = -.027$, $p = .435$).

Awakenings

A significant interaction did emerge for awakenings at 30 months of age ($\beta = -.082$, $p = .021$). Further exploration by gender revealed that this finding was significant for boys ($\beta = .048$, $p = .002$) but not for girls ($\beta = -.003$, $p = .856$). The results are presented graphically in Figure 8. Similarly, to the graphs presented for awakenings at 18 months of age, there was only a small difference in boys in the high vs. low reactivity groups when their mothers had not been depressed during pregnancy. Contrastingly, for boys whose mothers had been depressed antenatally, there was a large difference between boys in the high vs. low reactivity groups.

Sleep Problems

The regression model for sleep problems at 30 months did not reveal a significant depression X reactivity X gender interaction ($\beta = -.036$, $p = .305$).

Table 11: Summary of Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and a) sleep duration, b) number of night awakenings and c) sleep problems at 30 months, Step 4.

Variables	Total sleep Time		Awakenings		Sleep Problems	
	Step 4 R ² =.028		Step 4 R ² =.008		Step 4 R ² =.052	
	β	p	β	p	β	p
Step 1						
Postnatal Depression	.028	.041	.021	.131	.083	.000
Gender	-.078	.000	-.018	.100	-.018	.105
Ed. Qualification	-.014	.237	-.068	.000	-.079	.000
Alcohol	.027	.017	.000	.985	.033	.004
Smoking	-.030	.010	-.024	.041	.027	.020
Crowding	-.017	.158	.004	.752	-.015	.187
Marital Status	-.030	.011	-.011	.373	-.033	.005
Maternal Age	.134	.000	.035	.004	-.076	.000
Step 2						
Antenatal Depression	-.074	.040	.037	.305	.052	.150
Reactivity	.063	.074	-.043	.229	-.062	.076
Step 3						
Depression x Gender	.076	.030	-.011	.765	.053	.131
Depression x Reactivity	.046	.185	.100	.005	.051	.148
Reactivity x gender	-.062	.079	.045	.210	.054	.124
Step 4						
Depression x Reactivity x Gender	-.027	.435	-.082	.021	-.036	.305.
	F(14,7801)=16.236,p<.001		F(14,7862)=4.859,p<.001		F(14,7657)=31.130,p<.001	
	N=7,816		N=7,877		N=7,692	

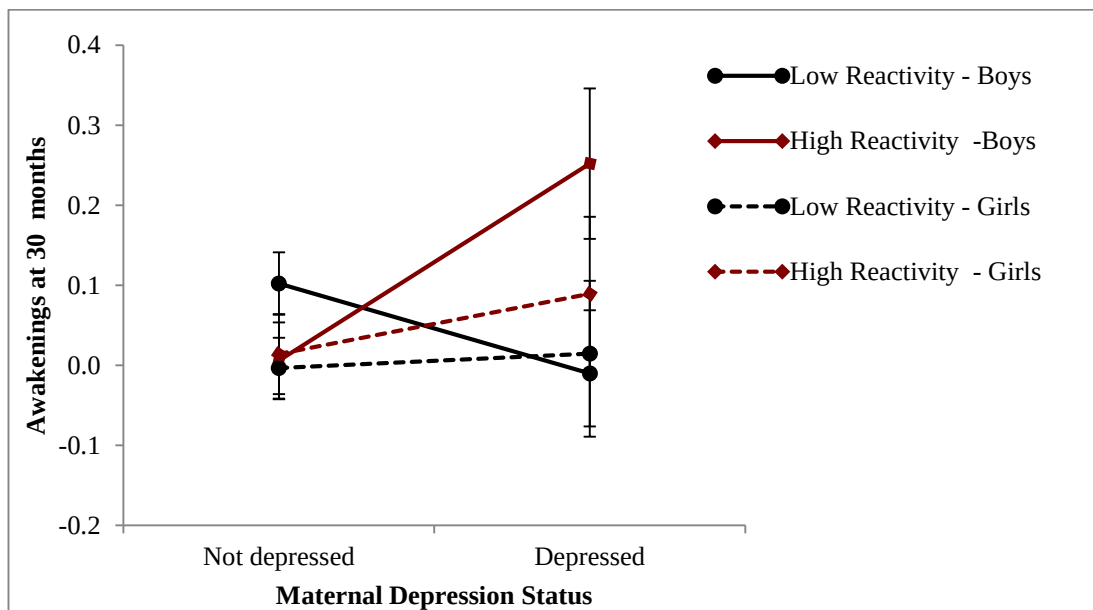


Figure 8: Association between antenatal depression and infant night awakenings at 30 months in boys and girls moderated by reactivity, using standardized residual scores, EPDS >12 for Depressed vs. Not depressed.

Summary of Findings

Reactivity moderated the association between antenatal depression and infant sleep for awakenings at 18 and 30 months of age and for sleep problems at 18 months of age. Boys in the high reactivity group exhibited a higher number of awakenings at 18 and 30 months and sleep problems at 18 months of age when they had been exposed to depression during pregnancy compared to all other groups.

2.3 STUDY II – GENERATION R

2.3.1 Methods

2.3.1.1 *Setting and Procedure*

The Generation R study is a population-based cohort investigating development and growth starting from the early stages of fetal life. The study is based in Rotterdam, The Netherlands. All women due to deliver from April 2002 to January 2006 were approached about participating in the study; 9,897 women were originally enrolled in the study and 7,295 were followed-up postnatally (Jaddoe et al., 2008; Jansen et al., 2011). The current sample consists of n=2,241 mothers, and their children for whom complete data was available. A detailed description of the methods of the Generation R cohort can be found elsewhere (Jaddoe, et al., 2008). The study was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam. Table 12 presents a brief comparison of the two cohorts, ALSPAC and Generation R.

2.3.1.2 *Participants*

Differences between the included and excluded sample (due to missing data) in the Generation R cohort were examined to ascertain whether attrition was selective. Women who remained in the study:

- a. Were slightly older;
- b. Had lower scores on the depression scale during pregnancy;
- c. Were more likely to have a university degree;
- d. Were more likely not to have smoked during pregnancy;
- e. Consumed less alcohol during pregnancy;
- f. Were more likely to be living with a partner or be married;
- g. Lived with fewer people in the household;
- h. Were more likely to be of Dutch/European background;
- i. Had a higher proportion of female infants;

The sample of Generation R is not ethnically homogeneous, with 75.8% of Dutch/European background compared to 98.6% White in ALSPAC. The remaining 24.2% (n=541) consists of 0.6% Indonesian, 1.3% Cape Verdian, 2.9% Moroccan, 2.3% Dutch Antillan, 5.7% Surinamese, 4.5% Turkish, 1.7% African, 2.3% American

(western and non-western), 2.5% Asian (western and non-western) and 0.3% Oceanic. Differences between ethnic groups on the key variables were examined and the two groups were found to be significantly different on all measures (Table 17, p.109). For that reason, some of the analysis (regression models) was repeated by ethnic group (Dutch/European vs. Other).

Finally, differences in sleep measures were examined. At 6 months participants for whom complete data was available slept longer and had more awakenings¹⁶. At 24 months the sample for whom complete data was available slept less and had more awakenings¹⁷.

A comparison in attrition between the ALSPAC and Generation R cohorts reveals similar characteristics for the remaining sample. In both cohorts the included sample with complete data were more likely to be married or living with their partner, have higher educational qualification, be older in age, live with fewer people in the household, report no smoking during pregnancy and score slightly lower on the depression scale during pregnancy. In both cohorts the majority of the sample reported White/European ethnicity. In Generation R, there was a lower percentage of boys in the remaining sample and a higher percentage of women reported drinking alcohol during pregnancy, two findings which were not evident in the ALSPAC cohort.

¹⁶ Complete data mean=10:55 SE=00:01 vs. 10:37 SE=00:01, $t(3985)=-7.0$, $p<.001$, sample with complete data 0 awakenings 40% vs. 43%, $\chi^2(3)=9.59$, $p=.022$

¹⁷ Complete data mean=11:34 SE=00:02 vs. mean=13:15 SE=00:02, $t(9841)=32.53$, $p<.001$, sample with complete data 0 awakenings 42% vs. 48% $\chi^2(3)=16.65$, $p<.001$

Table 12: Overview of the ALSPAC and Generation R cohorts and description of key variables

Cohort name (country)	Design	Original cohort	Number included in analysis n and % of original cohort	Antenatal depression	Infant reactivity	Infant sleep data
ALSPAC (UK)	prospective longitudinal study	n=14,062	8,991 (63.9%)	Mothers completed the EPDS at 32 weeks and 2 months postnatally	Maternal reports at 6 months using the Infant Temperament Questionnaire (scales of intensity, threshold, approach and adaptability).	Maternal reports at 6, 18 and 30 months Sleep Duration Night awakenings Sleep Problems
Generation R (NL)	prospective longitudinal study	n=9,897 n=7,285 followed- up postnatally	2,241/7,295(30.7%)	Mothers completed the Brief Symptom Inventory at 28 weeks and 2 months postnatally	Maternal reports at 6 months using the Infant Behaviour Questionnaire (IBQ) (scales of fear, recovery from distress and distress to limitations).	Maternal reports at 6 & 24 months. Sleep Duration Night awakenings

Table 13: Comparison of demographic characteristics of the current sample (n=2,241) and the whole Generation R sample (n=7,795).

	Sample for this study n=2,241	Overall Generation R Sample n=7,795	Test Statistic
<u>Variables</u>	n(%)	n(%)	
<u>Maternal characteristics</u>			
Marital Status			
Married/Living with Partner	91.8	87.3	$\chi^2(1)=62.16, p<.001$
Without partner	8.2	12.7	
Educational Qualification			
Secondary	65.3	73.2	$\chi^2=318.3, p<.001$
Degree	34.7	26.5	
Smoking during Pregnancy			
Yes	21.4	25.6	$\chi^2(1)=48.69, p<.001$
Alcohol during Pregnancy			
Yes	62.6	55.7	$\chi^2(1)=58.41, p<.001$
Age of mother (yrs)	mean=31.15, SD=4.44 (16.9-46.3)	mean=30.41, SD=5.2 (15.27-46.34)	
Crowding	mean =2.52, SD=.87	mean=2.64, SD=1.01	$t(6844)=5.82, p<.001$
Ethnic Group			
White	75.8	66.2	$\chi^2(2)=253.58, p<.001$
Depression during pregnancy	mean=0.16, SD=0.37	mean=0.23, SD=0.48	$t(6710)=12.76, p<.001$
Depression 2 months postnatal	mean =.19, SD=.41	mean=.22, SD=.46	
<u>Child characteristics</u>			
Child Gender			
Male	48.5	50.5	$\chi^2(1)=5.96, p=.015$
Reactivity score (standardized) mean	mean=-0.18, SD=2.17	mean =0.00, SD=2.27	
Fear	mean=0.37, SD=0.30	mean=0.39, SD=0.32	
Distress to limitations	mean=0.68, SD=0.32	mean=0.70, SD=0.32	
Recovery of distress (reflected)	mean=1.5,SD=0.29	mean=1.51,SD=0.30	

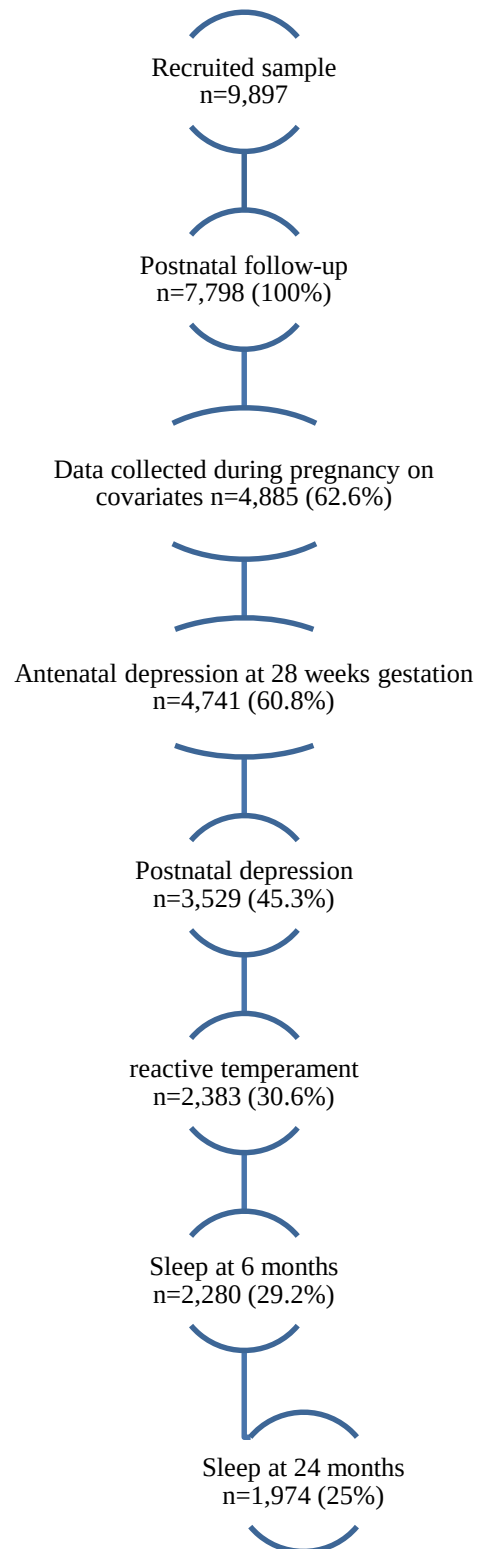


Figure 9: Diagram to illustrate attrition of data at each time point in the Generation R cohort.

2.3.1.3 Measures

2.3.1.3.1 Maternal Depression

Depression in Generation R was assessed using the Brief Symptom Inventory at 28 weeks gestation and 2 months postpartum (De Beurs, 2004; Derogatis & Melisaratos, 1983; Henrichs et al., 2010). The Brief Symptom Inventory is a validated self-report questionnaire assessing a range of psychiatric symptoms occurring in the week preceding the assessment (in this sample prenatal $\alpha=.86$, postnatal $\alpha=.85$). Answers range from 0 (not at all) to 4 (extremely). Only the depression subscale is used here (6 items, sum score ranging from 0 to 24). The values of items were summed and divided by the number of items answered.

2.3.1.3.2 Infant reactivity

Reactivity in Generation R was measured using a short version of the Infant Behaviour Questionnaire IBQ-R (Gartstein & Rothbart, 2003) at 6 months of age. A composite of reactivity was computed by standardizing and averaging the following three subscales (40 items): distress to limitations, fear and recovery of distress (reflected, Cronbach's α for reactivity score $\alpha=.87$). This construct has been previously used by Pluess and colleagues referred to as negative emotionality (Pluess, Velders, et al., 2010). A higher score reflects greater reactivity. For a comparison between the individual reactivity items in Generation R and ALSPAC see Appendix 1, page 276.

2.3.1.3.3 Infant Sleep

Infant sleep was assessed at 6 and 24 months of age via maternal reports. Mothers were asked to report on the average time their child had been going to bed and waking up in the preceding week. This information was used to calculate average sleep duration overnight¹⁸. They were also asked to report on the average number of night awakenings.

¹⁸ At 6 months, only data on sleep duration over the night hours was available, whereas at 24 months sleep duration for both the night hours and the 24-hour period were available. For within cohort consistency sleep during the night was utilized in the Generation R analysis. The analysis was repeated for sleep duration over the 24-hour period at 24 months of age and the results did not change.

2.3.1.3.4 Covariates

A number of variables were examined as covariates based on whether there were significant statistical associations between them and antenatal depression or any of the sleep variables. Information on maternal age, educational qualification, marital status, crowding, smoking, and alcohol consumption during pregnancy and infant gender were obtained through maternal report. These are the same covariates used in the previous analysis in the ALSPAC cohort.

2.3.1.4 Analysis Plan

Outliers ($z > |3.29|$) were Winsorised by replacing the outlying score with the next highest value (with $z < |3.29|$). First, descriptives for antenatal depression, sleep and reactivity were examined. Any differences in sleep by gender were tested for using independent t-tests. At this point differences in key variables (antenatal depression, reactivity and infant sleep) were also examined by ethnic background due to the varied composition of Generation R).

Second, bivariate associations were examined for sleep variables, antenatal depression, reactivity and the covariates (Pearson, two-tailed). Due to the large number of correlations undertaken, a conservative approach was also adopted here and Bonferroni correction for multiple testing was applied where possible. For section 2.3.2.4 there were 45 comparisons ($p = \alpha/n$ of correlations = $.05/45 = .001$ and so $p = .001$ and below were accepted).

Third, hierarchical regression models were then constructed to examine the moderating role of reactivity. The regression model consisted of 4 steps: Step 1 included all the covariates and gender, Step 2 included infant reactivity and antenatal depression, Step 3 included the 2-way interaction terms (depression X reactivity, depression X gender, reactivity X gender) and Step 4 included the 3-way interaction term antenatal depression X infant reactivity X gender. Due to the more limited number of regression analyses examined and the exploratory nature of the analysis, Bonferroni correction was not applied.

Similarly to the analysis in the previous study, all variables were centred on zero prior to running the regressions in accordance with recommendations by Aiken and West (1991). The moderator, reactivity, was found to be associated with antenatal depression and infant sleep. As this violates two of the assumptions of analysis with moderators,

this issue was addressed by regressing first reactivity on the sleep items and second on antenatal depression, which partials out the overlap between the moderator and the outcome and predictor, respectively. The residual terms for antenatal depression and sleep were used for the following analysis. The interaction terms were constructed using the aforementioned residual terms. All statistical analysis was carried out using SPSS version 20.0 (IBM, 2011).

2.3.2 Results

2.3.2.1 Treating the Data

The procedures outlined in section 2.2.2.1 were also followed here to deal with outliers and distribution issues.¹⁹

2.3.2.2 Descriptive Statistics

Descriptives for antenatal depression and reactivity are presented in Table 14.

Table 14: Descriptives for antenatal depression at 32 weeks and reactivity 6 months postpartum (n=2,383).

	Mean	SD	Range	Median
Antenatal depression	.16	.38	0-4	.00
Reactivity (standardized score)	-.14	2.2	-4.83-8.97	-.48

Descriptives for sleep data are presented in the table below ²⁰ (Table 15). Independent t-tests were used to examine gender differences for sleep duration and χ^2 tests for awakenings. At 6 months of age, no gender differences were found for sleep duration ($t(2278)=-.526$, $p=.599$). At the same time point there were significant differences in number of night awakenings $\chi^2(3)=20.21$, $p<.001$, with boys waking up more than girls (41.9% of boys had 0 awakenings compared to 49.3%). At 24 months of age boys slept on average less ($t(2007)=-3.54$, $p<.001$). In terms of night awakenings, no significant differences were found at 24 months of age $\chi^2(3)=1.85$, $p=.603$.

¹⁹ The following number of values was Winsorised for each variable: 6 month sleep duration (n=43), 24 month sleep duration (n=12), antenatal depression (n=17) and reactivity (n=5).

²⁰ A Kolmogorov-Smirnov test was performed and the sleep data were found to be non-normally distributed, D (2169) =.154, $p<.001$ for sleep duration at **6 months** of age; and D (1995) =.296, $p<.001$ for sleep duration at **24 months** of age.

Table 15: Descriptives for sleep data at 6 and 24 months of age.

	6 months of age			24 months of age		
Total sleep time (hh:min)						
	Boys	Girls	Total	Boys	Girls	Total
Mean	10:48	10:49	10:37	11:03	11:12	11:03
SD	01:19	01:25	01:22	00:47	00:49	00:48
Range	05:30-16:00	05:30-14:00	05:30-16:00	06:00-14:00	07:30-15:00	06:00-15:00
Median	11:00	11:00	11:00	11:00	11:00	11:00
Night awakenings n (%)						
Not once	458(41.9%)	568(49.3%)	1026(45.4%)	422(41.54%)	451(41.95%)	873(41.75%)
1 to 2 times	533(48.3%)	511(44.4%)	1044(46.28%)	529(52.07%)	568(52.84%)	1097(52.46%)
3 to 4 times	92(8.3%)	62(5.38%)	154(6.83%)	50(4.9%)	46(4.28%)	96(4.59%)
5 or more	21(1.9%)	11(0.096%)	32(1.4%)	15(1.4%)	10(0.9%)	25(1.2%)
Total	1104	1152	2256	1016	1075	2091

2.3.2.3 Differences in Sleep, Depression and Reactivity by Ethnic Background

Differences by ethnic background were examined on key variables of this analysis (Table 16). The two groups were found to be significantly different on all variables examined. Non-European participants slept less during both the 6 and 24-month assessments and had a higher number of awakenings. Mothers in the non-European group also scored higher on the depression scale and their infants scored significantly higher on the reactivity scale.

Table 16: Comparison of Dutch/European vs. non-European participants in Generation R study

Variables	Dutch/European		Non-European		Statistic
	N=1,700		N=541		
	Mean	SD	Mean	SD	
6 months					
Sleep Duration (hh:min)	10:47	01:30	10:09	01:44	t(2241)=8.00, p<.001
Awakenings	1.61	0.68	1.71	0.65	t(2169)=-3.09, p=.002
24 months					
Sleep Duration (hh:min)	11:07	00:49	10:42	01:12	t(1882)=8.12, p<.001
Awakenings	1.62	0.62	1.76	0.65	t(1949)=-3.76, p<.001
Prenatal depression	0.12	0.30	0.30	0.51	t(2241)=-9.7, p<.001
Reactivity	-0.52	2.0	0.92	2.41	t(2241)=-13.81, p<.001

2.3.2.4 Correlational Analyses

Correlations of sleep variables are examined in Table 17²¹. Correlations were in the expected direction with positive associations between sleep duration at 6 months and 24 months ($r=.171$, $p<.001$) and awakenings at 6 and 24 months ($r=.173$, $p<.001$). There was a negative association between sleep duration and awakenings at 6 months ($r=-.088$, $p<.001$) and 24 months ($r=-.227$, $p<.001$).

²¹ Bonferroni correction $p=\alpha/n$ of correlations $=.05/45=.001$

Table 17: Unadjusted bivariate associations of sleep variables at 6 and 24 months

	1	2	3	4
1. Sleep duration at 6 months	_____			
2. Number of awakenings at 6 months	-.088**(.000)	_____		
3. Sleep duration at 24 months	.171**(.000)	-.165**(.000)	_____	
4. Number of awakenings at 24 months	-.020(.235)	.173**(.000)	-.227**(.000)	_____

**. Correlation is significant at the 0.01 level (2-tailed). N=1820

Correlations between sleep variables and the moderator, reactivity, and the covariates were examined in Table 18. Antenatal depression was associated with decreased sleep duration at 6 and 24 months of age and with a higher number of awakenings at 24 months but not at 6 months of age. Reactive temperament was associated with decreased sleep duration and increased number of awakenings at both time points. (Bonferroni correction $.05/36=.00138$).

Table 18: Unadjusted associations between sleep variables at 6 and 24 months and reactivity, depression scores and covariates.

	Sleep duration at 6 months	Number of awakenings at 6 months	Sleep duration at 24 months	Number of awakenings at 24 months
Antenatal Depression	-.076**(.001)	.025 (.283)	-.077**(.001)	.093**(.000)
Postnatal Depression	-.034(.150)	.020(.398)	-.071**(.002)	.057(.015)
Reactive Temperament	-.170**(.000)	.345**(.000)	-.227**(.000)	.196**(.000)
Ed. Qualification	.042(.075)	.019(.413)	.064**(.006)	-.078**(.001)
Alcohol	.062**(.008)	-.031(.192)	.091**(.000)	-.049*(.038)
Smoking	.026(.275)	-.054*(.021)	.013(.568)	.027(.243)
Crowding	-.027(.243)	.080**(.001)	.007(.769)	.035(.135)
Marital Status	-.054*(.022)	-.008(.729)	-.061**(.010)	.065**(.006)
Maternal Age	.002(.944)	.050*(.032)	-.023(.337)	.013(.587)

**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed). N=1820

2.3.2.5 Moderator analysis

2.3.2.5.1 Sleep at 6 months of age: Does reactivity moderate the association between antenatal depression and infant sleep at 6 months of age (total sleep time and awakenings)?

Total Sleep Time

There was no evidence at 6 months of age that reactivity or gender acted as moderators of the association between antenatal depression and infant sleep duration ($\beta = -.001$, $p = .957$). Analysis was repeated in the Dutch/European sample only to match the sample composition in the ALSPAC cohort. No differences were found in the results ($\beta = .029$, $p = .274$).

Awakenings

There was also no evidence of a moderating effect for night awakenings ($\beta = -.023$, $p = .298$). The results did not change when the analysis was repeated for the Dutch/European sample only ($\beta = -.045$, $p = .093$).

Table 19: Summary of Hierarchical Regression Model testing the moderating effect of reactivity and gender on the association between antenatal depression and infant sleep at 6 months of age for sleep duration and number of night awakenings.

	Sleep duration at 6 months		Awakenings at 6 months	
Variables	β	p	β	p
Step 1				
Postnatal Depression	-.005	.831	-.008	.728
Gender	.013	.555	-.109	.000
Ed. Qualification	.022	.380	.019	.453
Alcohol	.044	.056	-.026	.271
Smoking	.036	.100	-.034	.128
Crowding	-.019	.392	.073	.001
Marital Status	-.065	.003	.023	.293
Maternal Age	-.011	.633	.065	.007
Step 2				
Antenatal Depression	-.036	.138	.023	.357
Reactivity	.012	.583	.010	.650
Step 3				
Depression x Gender	-.001	.961	.020	.373
Depression x Reactivity	-.015	.474	.032	.135
Reactivity x Gender	-.006	.776	-.024	.259
Step 4				
Depression x Reactivity x Gender	.001	.957	-.023	.298
	$R^2 = .011$		$R^2 = .027$	
	$F(14,2226) = 1.7, p = .049$		$F(14,2154) = 4.27, p < .001$	
	$n = 2,241$		$n = 2,169$	

2.3.2.5.2 Sleep at 24 months of age: Does reactivity moderate the association between antenatal depression and infant sleep at 24 months of age (total sleep time and awakenings)?

Total Sleep Time

Findings at 24 months of age for sleep duration, revealed a significant 3-way interaction ($\beta=.053$, $p=.034$ – see Table 20) which, when further explored, was found to be in different directions for girls and boys ($\beta=.063$, $p=.053$, and $\beta=-.027$, $p=.422$ respectively).

Analysis for sleep duration at 24 months was repeated according to ethnic group (Dutch/European participants vs. Non-European) to match the predominantly White ethnic background of participants in the ALSPAC cohort. Findings from Dutch/European participants only in the Generation R cohort ($n=1,539$) revealed a significant 3-way interaction ($\beta=.067$, $p=.018$) which, when further explored, was found to be significant for boys ($\beta=-.110$, $p=.003$), but not for girls, ($\beta=.009$, $p=.828$). These findings are presented graphically in Figure 10, page 114. Highly reactive boys slept less when exposed to antenatal depression compared to low reactivity boys. This finding is in line with results from the ALSPAC cohort.

When the analysis was repeated for the non-European group ($n=359$) the 3 way interaction was no longer found to be significant ($\beta=-.051$, $p=.477$).

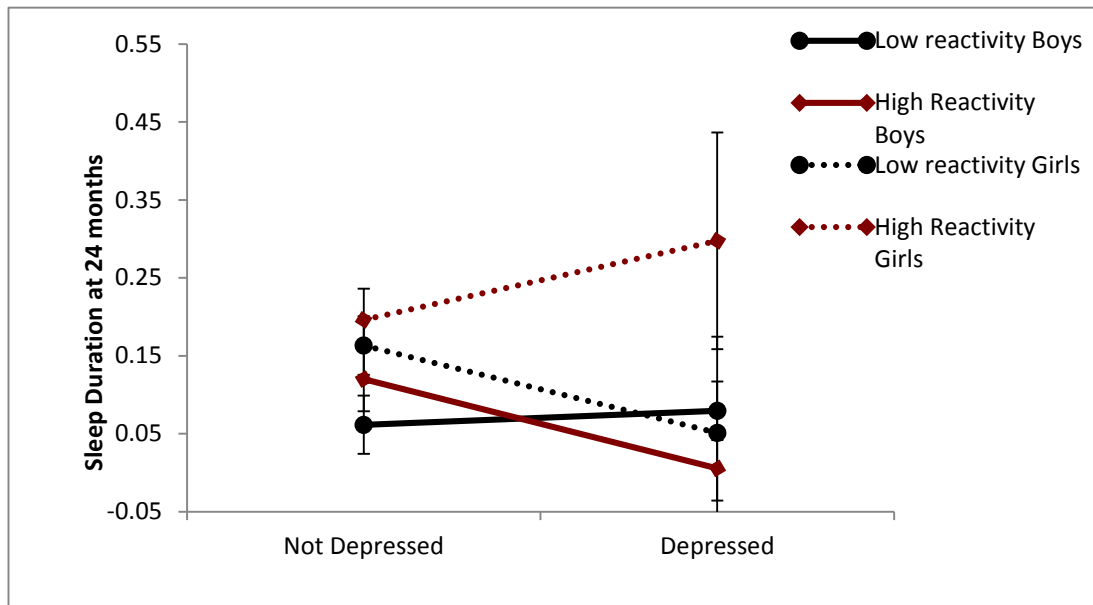
Awakenings

There was no evidence that infant reactivity was a moderator of the association between antenatal depression and night awakenings at 24 months ($\beta=-.033$, $p=.172$, Table 20). Analysis with the Dutch/European sample only, revealed a similar finding ($\beta=-.021$, $p=.436$).

Table 20: Summary of Hierarchical Regression Model testing the moderating effect of reactivity and gender on the association between antenatal depression and infant sleep at 24 months of age for sleep duration and number of night awakenings.

Variables	Generation R			
	Sleep duration at 24 months		Awakenings at 24 months	
Step 1	β	p	β	p
Postnatal Depression	-.013	.616	.003	.919
Gender	.090	.000	-.027	.231
Ed. Qualification	.039	.139	-.070	.007
Alcohol	.076	.002	-.024	.323
Smoking	.025	.299	.000	.995
Crowding	.037	.123	.009	.714
Marital Status	-.056	.017	.055	.017
Maternal Age	-.086	.001	.051	.039
Step 2				
Antenatal Depression	-.031	.250	.068	.010
Reactivity	.006	.792	-.011	.639
Step 3				
Depression x Gender	.031	.218	-.025	.298
Depression x Reactivity	.032	.165	.016	.476
Reactivity x Gender	.001	.963	-.007	.752
Step 4				
Depression x Reactivity x Gender	.052	.034	-.033	.172
	R ² =.029		R ² =.018	
	F(14,1882)=3.98, p<.001		F(14,1959)=2.5, p=.002	
	N=1,898		n=1,974	

Figure 10: Association between antenatal depression and infant sleep duration in boys and girls, moderated by reactivity in the Dutch/European sample, using standardized residual scores, Depressed category top 15% of scorers.



Summary of Findings

There was evidence that reactivity moderated the association between antenatal depression and infant sleep for sleep duration at 24 months. Analysis was repeated by ethnicity. The Dutch/European group of boys in the high reactivity group exhibited the longest sleep duration when they had not been exposed to antenatal depression and the shortest sleep duration when they had been exposed. Analysis in the whole sample revealed weak evidence for a depression X reactivity interaction for girls but not for boys.

2.4 DISCUSSION

The present study used two large prospective longitudinal cohorts to examine whether infants reactive temperament acted as a moderator of the association between antenatal depression and infant sleep. The findings suggest that infant reactivity did act as a moderator of this association. Whilst not consistent on every outcome measure, a moderating effect was found for awakenings at 18 and 30 months of age in the ALSPAC cohort, with boys in the high reactive temperament group displaying a higher number of awakenings when previously exposed to antenatal depression. A similar finding emerged for sleep problems at 18 months in the ALSPAC cohort, where infant reactivity was found to moderate the association between antenatal depression and sleep problems. The findings were again more prominent for boys and further exploration indicated that highly reactive boys were more at risk for sleep problems in the context of antenatal depression.

The association between antenatal depression and sleep duration at 24 months of age in the Generation R cohort was also moderated by reactivity. When the analysis was restricted to include Dutch/European participants only, to more closely match the composition of participants in the ALSPAC cohort, a significant 3-way interaction was found. Reactive boys exhibited shorter sleep duration in the context of high antenatal depression. Analysis with the whole sample revealed an additional finding for girls, which was not found in the Dutch/European-only group or in ALSPAC. In the context of high depression scores, girls in the low reactivity group exhibited shorter sleep duration whereas girls in the high reactivity group exhibited the opposite pattern with longer sleep duration. This pattern is in contrast to the findings in boys and to the hypothesis formulated in the introduction section. As no findings were evident for girls in the ALSPAC cohort, which was ethnically homogeneous it may be speculated that this finding is related to the addition of participants who are ethnically and culturally dissimilar to the rest of the population. As this finding was only present when using a larger sample size it also highlights the sensitive nature of interaction models and warrants for cautious interpretation of the findings.

All the findings held after controlling for a number of important covariates, including postnatal depression, and after partialling out the effects of infant reactivity on antenatal depression and on the sleep variables.

2.4.1 Setting the findings in context

This is the first time that reactivity has been studied as a moderator of the association between antenatal depression and infant sleep. The findings are in line with a growing body of evidence that highlights that some individuals are more susceptible to environmental influences (Bakermans-Kranenburg & Van IJzendoorn, 2007; Ellis, et al., 2011; Pluess & Belsky, 2009, 2010, 2011; Ramchandani, van IJzendoorn, & Bakermans-Kranenburg, 2010; Velderman, et al., 2006). Indeed there is an increasingly strong suggestion that children with reactive temperamental characteristics may be more susceptible than others to the effects of both positive and negative environmental influences (Ellis, et al., 2011). This study adds to this literature and supports the role of infant reactivity as a potential marker of differential susceptibility to environmental influences.

With the majority of evidence on differential susceptibility surfacing from studies during the postnatal period, this study adds to only a handful of reports investigating the potential effects of antenatal mental health (Pluess, Velders, et al., 2010). The findings presented here highlight an increased vulnerability for boys with reactive temperament to environmental influences and stressors, such as antenatal depression, even during the very early stages of life. Highly reactive boys exposed to maternal depression exhibited shorter sleep duration, a higher number of night awakenings and sleep problems. These results, interpreted in line with the programming hypothesis are suggestive of a more vigilant sleep profile.

An interesting finding that emerged from this analysis was that the moderating effect of temperament, on the association between antenatal depression and infant sleep, might be affected by culture or ethnic background. This finding emerged only in the Generation R cohort, where 75% of sample was White and 25% was ethnically diverse, as the ALSPAC sample presents with little variety in ethnic background with 98% of the sample being White/European. Ethnicity has not yet been adequately explored in the context of differential susceptibility or in terms of the effects of antenatal depression on child development. Differences in ethnic background though with regards to sleep have been reported extensively. Studies from the US reported African- American Hispanic children to take more and longer naps and to sleep less at night compared to White children (Crosby, LeBourgeois, & Harsh, 2005; Lavigne et al., 1999; Nevarez, et al., 2010). Milan et al. (2007) examined another US sample and found ethnic differences in

how mothers manage and perceive children's sleep. For example, children in ethnic minority families are more likely to sleep with a parent and less likely to sleep in their own room compared to children in White families. A recent review further highlights these differences and suggests that children of Asian countries had shorter sleep duration (on average 1 hour) (Galland, Taylor, Elder, & Herbison, 2012).

2.4.1.1 *Criteria for Differential Susceptibility*

The findings indicate a differential moderating effect of infant reactive temperament on the association between antenatal depression and infant sleep. The results presented here meet 4 criteria for differential susceptibility: first, statistical manipulation of the data meant that reactive temperament was unrelated to both the outcome, infant sleep, and the predictor, antenatal depression (Criteria 2 & 3 of differential susceptibility as presented in p. 64). Although this was not the case at the first stage of analysis, statistical manipulation allowed for the residual terms to be added in the regression models thus, meeting the above criteria, without changing the results. Second, the slopes of infant sleep for boys were significantly different to zero. Third, the criteria indicate that the slope for the susceptible group (highly reactive temperament) is significantly steeper than the slope for the non-susceptible group (low reactive temperament), which was confirmed by the graphs (p.95, p. 98 and p. 114). Finally, a genuine cross-over interaction was confirmed by the graphs (Criteria 1, p. 64). In this analysis it is difficult to truly find differential susceptibility, as maternal depression cannot be measured on a continuum of positive to negative rather it is measured on a continuum of negative to absence of negative.

2.4.2 *Strengths and Limitations*

The study has a number of key strengths. The study employs two large prospective longitudinal birth cohorts to examine these questions, based in two different European countries, the Netherlands and the UK. Although the cohorts are independent it has been possible to use broadly comparable measures for the assessment of maternal depression, sleep and temperament as well as for the covariates included in the analysis. The broad similarity of the findings across the two cohorts allows some confidence to be drawn about the veracity of the findings. The longitudinal and prospective design of the studies also allows for some cautious inferences to be made about the direction of the effects.

It has been noted that power to detect interactions is lower than power needed to detect main effects, and that interactions in particular, may be more sensitive to the scales used (Aiken and West, 1991; McClelland and Judd, 1993), which might result in a higher number of positive findings due to Type I error (Duncan and Keller, 2011). The consistency of our results across two cohorts, using comparable but not identical scales, provide evidence that these findings are not likely to be due to Type I error.

The study employed widely used and well-established measures for the assessment of maternal depression and infant temperament.

Finally, large prospective studies of normal, non-clinical populations, such as the ones examined here to a large extent avoid selection bias, unlike clinical studies. Therefore, our findings are potentially generalizable despite considerable non-response (for example, in the Generation R study).

It is important to acknowledge some of the limitations of this study. As this analysis was conducted on pre-established birth cohorts it was not possible to design the assessments of sleep to occur at identical time points. Some assessments did occur at comparable time points across the two cohorts (6 months). However, subsequent sleep assessment occurred at 18 and 30 months for ALSPAC compared to 24 months for Generation R study. Comparison across the same developmental age might have revealed results that were more comparable across cohorts, particularly considering the rapid developmental changes that occur in infant sleep in the early years of life.

It was not possible to use identical measures of infant temperament. The two measures however, do share a large number of common characteristics and attributes (see Appendix 1 p. 276). Questionnaire items, which tapped into the construct of reactive temperament, were independently identified. Both constructs across cohorts show good internal consistencies.

All data was collected through maternal report and is therefore subject to response bias. The mother is nevertheless an ideal observer of her infant's sleep profile, due to extensive contact with him/her; this allows for a variety of sleep characteristics and habits to be observed and reported (for example see Sadeh, 2004a).

The statistical analyses and study design implemented here, although longitudinal in design, do not permit clear causal inferences. They do give useful temporal information as it is unlikely that infant reactivity can affect antenatal depression.

In the first steps of analysis it was established that the moderator was weakly associated with both the predictor and outcome. This is not ideal for moderator analyses. However, following the partialling out of the small overlap between temperament and sleep, in accordance with recommendations for moderator analysis, this issue was addressed using the best available method.

Finally, every effort was made to ensure that the coding of sleep data was conducted in the same way across cohorts, with the same rules applying for dealing with outliers and for Winsorising.

2.4.3 Conclusion

This is the first study to provide empirical evidence that the association between antenatal depression and infant sleep is moderated by reactive temperament. This association between antenatal depression and infant sleep was more pronounced in boys in the high reactivity group. Offspring characteristics might increase an individual's vulnerability to negative environmental influences, such as antenatal depression, even during fetal life.

Chapter 3: Antenatal depression and
infant sleep; examining the potential
moderating effect of the serotonin
transporter promoter polymorphism

3 Chapter Overview

The previous chapter determined that infant temperamental reactivity did moderate the association between antenatal depression and infant sleep in two cohort studies. This chapter examines whether genes can also act as moderators of this association. More specifically, the present study investigates the role of the serotonin transporter promoter polymorphism (5-HTTLPR) as a potential moderator of the association between antenatal depression and infant sleep.

This chapter examines this gene X environment interaction (GxE) in two independent longitudinal cohorts; the ALSPAC and Generation R studies. Infant sleep was assessed at 3 time-points 6, 18 and 30 months of age in the ALSPAC cohort and at 6 and 24 months of age in the Generation R cohort. As in the previous chapter, this chapter examines three characteristics of infant sleep: sleep duration, number of night awakenings and sleep problems.

This is the first study to examine the moderating role of 5-HTTLPR on the association between antenatal depression and infant sleep. The chapter briefly describes the serotonergic system, the role of serotonin in the regulation of the sleep-wake cycle and evidence regarding GxE in sleep studies, before addressing the aims of this chapter. A brief description of the methods, which are similar to those in Chapter 2, is followed by the results. Hierarchical linear regressions are used. The chapter concludes with a discussion of the findings and strengths and limitations of the study.

3.1 INTRODUCTION

3.1.1 The serotonergic system

Serotonin (5-hydroxytryptamine, 5-HT) was discovered more than 50 years ago (Amin, Crawford, & Gaddum, 1954) and is now understood to be an important neurotransmitter affecting both psychological and physiological processes. It is also known to play a pivotal role in the regulation of activity of the central nervous system (CNS). The serotonergic system extends throughout the brain and CNS. Serotonin is concentrated in the raphe nuclei of the midbrain and brainstem.

The serotonergic system impacts on almost every aspect of the mammalian physiology. Examples include cardiovascular activity, respiration, pain sensitivity and thermoregulation (Monti, 2011). In addition, serotonin is associated with more centrally controlled functions such as circadian rhythm/ sleep states, appetite, aggression, mood, cognition, memory and learning (Sodhi & Sanders-Bush, 2004). As a result, drugs with serotonergic activity are currently used for a range of psychiatric disorders including schizophrenia, depression, anxiety and eating disorders (Sodhi & Sanders-Bush, 2004).

There is evidence to suggest that serotonin and serotonergic gene expression will not only influence behaviour but may also be substantially implicated in the pathogenesis of neuropsychiatric disorders, although the exact mechanisms of transmission of risk are not fully understood (Leonardo & Hen, 2006; Sodhi & Sanders-Bush, 2004).

The development of the serotonergic system starts during the first trimester of pregnancy and continues to develop until at least the end of the first year of life (Kinney, Belliveau, Trachtenberg, Rava, & Paterson, 2007). Serotonergic neurons can be detected as early as embryonic day 5, and by 15 weeks clustering of cell bodies in the raphe nuclei can be observed (Sodhi & Sanders-Bush, 2004). Serotonin levels increase in the first 2 years of life and then start declining. By age 5 they have declined to adult levels.

In early development serotonin acts as a regulator of brain development. It acts as a growth and as a trophic factor (Oberlander et al., 2010). As a growth factor it regulates the development of neural systems and as a trophic factor it regulates important activities during brain development and plasticity (for example cell division, differentiation and migration, growth and development (Frodl et al., 2004; Gould,

1999). 5-HT has been identified as central to the development of the HPA axis (Oberlander, et al., 2010).

Serotonin also influences a number of functions such as appetite and mood and plays a key role in the development of many neurotransmitter pathways. It follows therefore, that any disturbances to the development and functioning of the serotonergic system may contribute to the development of disorders. For example anxiety and depression are two psychiatric disorders where pharmacological evidence supports a role for serotonin.

3.1.1.1 *Synthesis of Serotonin*

Serotonin is synthesized from the amino acid tryptophan. The majority of serotonin (90%) is located in the gut where it regulates intestinal movement (Berger, Gray, & Roth, 2009). The remaining 10% is produced in the raphe nuclei groups, which is the main source of 5-HT in the brain. Serotonin is then transported to the limbic system, hippocampus and hypothalamus within 5-HT neurons. It is hydroxylated by tryptophan monooxygenase, which produces 5-hydroxy-tryptophan (5-HTP) in the axon nerve terminal where the enzyme aromatic L-amino acid decarboxylase catalyses the tryptophan metabolite from 5-HTP into 5-HT.

3.1.2 The serotonin transporter (5-HTT)

Neurotransmission of serotonin is terminated by the removal of 5-HT from the synaptic cleft mostly by re-uptake into the presynaptic cell via the serotonin transporter (5-HTT). At least 15 distinct types of receptors have been identified for the serotonergic system: seven 5-HT receptor families (5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, 5-HT₇) and several 5-HT receptor subtypes.

3.1.3 Genetics of the serotonin transporter (SLC6A4)

The serotonin transporter gene (SLC6A4) is located on the long arm of the 17th chromosome (17q11.1-q12). Variations of a polymorphism in the promoter region of the serotonin transporter (5-HTTLPR) are of interest here. The length variation is a 43bp insertion/deletion polymorphism and consists of two common variants in the transcriptional control region of the serotonin transporter (5-HTT). In the case of the short 's' allele, the 43 bp sequence is deleted leading to 14 repeat elements and in the long 'l' allele the 43 bp sequence results in 16 repeat elements. The long allele of the polymorphism shows increased transcriptional efficiency (more 5-HTT mRNA and

protein produced), 5-HTT expression and 5-HTT re-uptake in comparison to the short allele (Frodl, et al., 2004; Heinz et al., 2000; Lesch, 2001; Lesch et al., 1996). In carriers of the 's' allele this would result in increased concentration of serotonin at the synaptic cleft, compared to carriers of the 'l' allele, resulting in increased stimulation of the postsynaptic neuron. In addition to the 's' and 'l' polymorphic variations (bi-allelic classification), an A vs. G single nucleotide polymorphism (SNP) within the repetitive region that constitutes the 5-HTTLPR (dbSNP: rs25531) has been identified and is present in the 'l' allele. The L_G allele results in decreased 5-HTT transcription compared to L_A , thus making it functionally equivalent to the 's' allele (tri-allelic classification) (Hu et al., 2005). Individuals have two copies of the serotonin transporter, one on each of their maternally and paternally inherited chromosomes (Brzustowicz & Freedman, 2011). Where tri-allelic classification is possible individuals homozygous for the L_G allele or carrying the SL_G alleles are classified as having low activity alleles along with those homozygous for the 's' allele.

3.1.4 Serotonin and sleep

In Chapter 1 (section 1.2.1.1) the two-process model of sleep was described. Process 'S' is the homeostatic process that regulates propensity to sleep. If some 5-HT neurons are implicated in process 'S' it follows that they should be most active during waking and inactive during sleep. There is now evidence to suggest that sleep deprivation is followed by increase in delta-wave sleep and the impairment of 5-HT synthesis during deprivation suppresses the subsequent rebound of slow wave sleep (Sallanon, Janin, Buda, & Jouvet, 1983). It is hypothesized that some 5-HT neurons, firing regularly during waking, are part of the 'S' process and measure the intensity and duration of waking.

Insomnia inducing lesions in the raphe system or the pre-optic area further implicate 5-HT and the pre-optic area in sleep mechanisms (Jouvet, 1999; McGinty & Serman, 1968)²². Research from animals, specifically on sleep stage characteristics and serotonin receptor subtypes suggests that mice lacking functional 5-HTT and 5-HT_{1A} receptors display more REM sleep compared to wild type littermates (Monaca, Boutrel, Hen,

²² A study by Zeitzer (2002) also reports an ultradian variation of ventricular 5-HT concentration throughout NonREM and REM sleep. This evidence put together suggests that serotonergic transmission stimulates wakefulness.

Hamon, & Adrien, 2003; Wisor, et al., 2003). Furthermore, reduction of 5-HT₂ receptor activity increased SWS and SWA connecting these receptors to SWS regulation (Landolt et al., 1999). Finally administration of SSRIs was associated with decrease in SWS and REM sleep, increase in stage 1 and 2 sleep and to poorer quality of sleep as measured by polysomnography (PSG) (Oberndorfer, Saletu-Zyhlarz, & Saletu, 2000).

3.1.5 Gene x Environment Interaction

3.1.5.1 *Interaction of early life stress and 5-HTTLPR*

Over the last decade, GxE interaction studies have been very prominent in psychiatric and mental health research. Findings which suggest that genes and environment interact to predict development have been in the spotlight. This section gives a brief overview of the field over the last 10 years and discusses some of the methodological and statistical issues that have been raised regarding GxE research. For this chapter, the definition of GxE interaction by Thomas is used to describe the ‘joint effect of one or more genes with one or more environmental factors that cannot be readily explained by their separate marginal effects’ (Thomas, 2010, p. 259).

An increasing number of studies suggest that gene x environment interactions might play an integral part in the aetiology of emotional and behavioural problems and the subsequent development of psychiatric disorders. In 2003, a seminal paper was published in *Science* by Caspi, Moffitt and colleagues (Caspi et al., 2003). This prospective longitudinal study tested whether a functional polymorphism of the serotonin transporter gene (5-HTTLPR) moderated the association between stressful life events, occurring early in life, and adult depression. The results indicated that individuals with at least one copy of the short allele were at higher risk for depression and suicidality compared to individuals homozygous for the long allele, if exposed to a stressful life event early in life. To date, the paper by Caspi and Mofitt has been cited 3,370 times²³ and has generated a great deal of interest around the potential of GxE interaction studies. It has also led to an extended debate on issues relating to conducting and reporting of GxE studies. Over 55 studies have attempted to replicate this finding and to extend these findings to a variety of outcomes and environmental influences. The three meta-analyses that followed have also attempted to clarify the role of 5-HTTLPR

²³ The number of citations was reported by Scopus on Aug. 31st, 2013.

as a moderator of early life stress and later development; however, they have produced conflicting findings, and it remains to be determined whether, and under what circumstances, 5-HTTLPR might moderate early life stress and adult depression (Karg, Burmeister, Shedden, & Sen, 2011; Munafò MR, Durrant C, Lewis G, & J., 2009; Risch et al., 2009).

The debate triggered by the conflicting evidence on this topic, has led to a number of very important issues being considered, including methodological issues regarding interaction effects and criteria for reporting of GxE studies (Duncan & Keller, 2011; Dunn et al., 2011; Little et al., 2009). A significant portion of the debate has also been concerned with the inclusion and exclusion criteria for the studies used in the meta-analyses. For example, out of the 55 replication studies identified by Karg and colleagues in 2011, Munafò et al. included only 5 and Risch et al. included 14 (Karg, et al., 2011; Munafò MR, et al., 2009; Risch, et al., 2009). As discussed by Karg et al., the reasons why only a subset of the studies were included in the first two meta-analyses are as follows: first, primary data was unavailable at the time; second, there was a narrow focus on 5-HTTLPR and stressful life events (SLEs) in the development of depression, compared to the meta-analysis by Karg et al., for example, which included studies examining maltreatment and medical conditions as indicators of stress in early life. The most recent of these meta-analyses reported an increased risk for carriers of the S allele to develop depression when exposed to childhood maltreatment and specific medical conditions (Karg, et al., 2011). A significant although weaker effect was also found in the case of stressful life events (SLEs).

3.1.5.2 Methodological Issues in GxE research

Three aspects of the GxE debate in psychiatry are discussed here: first, assessment of exposure; second, sample size and statistical power to detect interaction effects; and third, the issues of heterogeneity and replication.

The assessment of exposure refers to the stressor under examination, childhood maltreatment, medical conditions or, here, antenatal depression. There are four key concerns.

- Exposure to these stressors will be of varying intensity amongst individuals and the effects may well vary with prolonged exposure.

- These stressors are often multidimensional, with the potential to affect a number of development outcomes and trajectories, which could include cognitive, physiological, emotional and behavioural development and even language development.
- Age of exposure may also be an important factor to consider, as a stressor may have more detrimental effects if sustained at one developmental time point compared to another.
- It is also important to bear in mind that assessment of exposure will rarely be free of measurement error. The scales used therefore, may also impact on the findings (Duncan & Keller, 2011).

Sample size and statistical power has been discussed by Duncan and Keller, who demonstrate the sample size needed to detect moderate ($r^2=0.001$), large ($r^2=0.01$) and very large ($r^2=0.1$) GxE effect sizes²⁴. A critical conclusion reached is that most of the GxE studies published so far have been underpowered (Duncan & Keller, 2011). For example, even for large effect sizes, samples in excess of 600 would be needed, whereas most studies are far smaller than this. For this reason Duncan and Keller conclude that at this point true, adequately powered replications of studies such as the one by Caspi, Moffitt and colleagues would be more important and helpful in clarifying the role of 5-HTTLPR compared to novel investigations.

The third point concerns the heterogeneity of studies and replication. A number of factors need to be closely evaluated to determine whether a study is a true replication, including: the phenotypic variable; the genetic polymorphism examined; the environmental moderators; the statistical analysis undertaken; the confounders included, and the gender differences reported. These are all factors which can cause inconsistencies in the findings due to differences in methodology and data quality, and thus may cause confusion (Thomas, 2010).

²⁴ These estimates are based on the assumption there is no error in measurement and that the environmental and genetic variables account for 20% and .5% of the variance in the outcome variable respectively, p4 – see figure below

3.1.5.3 Genetic Variation of 5-HTTLPR and sleep

While there exists a great variability amongst individuals in terms of sleep and sleep-wake regulation, sleep within individuals seems to be relatively stable and trait-like. This has led to the assumption and subsequently to evidence that sleep-wake behaviour and circadian rhythms are partly genetically controlled (Wulff, et al., 2009). There is good evidence from twin studies showing higher concordance rates in monozygotic compared to dizygotic twins and unrelated subjects with respect to sleep stages 2 and 4 and delta sleep (Linkowski, 1999). Evidence, however, on specific gene variants accounting for sleep behaviour is limited (Andretic, et al., 2008). A number of studies have focused on the role of clock genes in differences in sleep but only a limited number of studies have examined the role of 5-HTTLPR on sleep. Due to the limited number of studies examining a GxE interaction with 5-HTTLPR, studies addressing main effects of 5-HTTLPR on sleep are also discussed here.

Brummett and colleagues (2007) examined the effects of 5-HTTLPR genotype on sleep quality in individuals who were caring for a relative with Alzheimer's disease or other dementia (n=142), and in a group of controls (n=146). The majority of the sample (74.6%) was female and 30% were African- American. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). Caregivers reported significantly poorer sleep quality. A significant two-way interaction of caregiver status x allele group revealed that individuals homozygous for the 's' allele reported worse sleep compared with all other groups. Analysis of specific aspects of sleep using the PSQI components indicated a significant interaction effect of caregiver status x genotype for scores on latency (time to fall asleep), and sleep disturbances, and was marginally associated with sleep efficacy and problems with daytime functioning. It is worth noting, that the study used a bi-allelic classification (ss, sl, ll) of 5-HTTLPR and included African-American participants in the analysis, despite the evidence suggesting that 5-HTTLPR may function differently amongst ethnic groups.

Deuschle and colleagues (2010) examined the frequency of the s allele in individuals diagnosed with primary insomnia. 157 individuals fulfilled DSM-IV criteria for chronic primary insomnia and psychophysiological insomnia for a period of at least 6 months. All participants underwent PSG for two nights and were of White-Caucasian background. A randomly selected sample of 836 served as the control group. Genotype distribution was within Hardy-Weinberg equilibrium. The frequency of the s allele in

patients with insomnia was highest compared to other groups and this result was found to be statistically significant (47.1% ss vs. 39.9 sl, ll). When the analysis was repeated for males and females separately, the results remained significant for females. Results held in posthoc analysis with the exclusion of patients with a differential diagnosis of affective disorders and patients of non-German descent.

Barclay and colleagues (2011) found a significant main effect of 5-HTTLPR on mean sleep quality in a sample of 947 adolescents. Individuals homozygous for the 'l' allele reported poorer quality of sleep than carriers of at least one 's' allele. The authors further analyzed for gender differences and found the effect to be significant only for males. This study contrasts with the other studies identifying the 's' allele as the risk allele associated with negative outcomes. The authors discuss a number of factors which may have affected their results including their sample composition (students who might have had more chaotic lifestyles compared to non-students) and seasonal effects.

The functional polymorphism of 5-HTT and normal sleep in humans was examined in a sample of 54 by Linn and colleagues (2007). Using the bi-allelic classification of the serotonin gene, the authors reported genotype frequency to be comparable to general population, although no statistical test is provided. Analysis of data from PSG, controlling for age and sex, revealed that individuals with the 's' allele (ss +sl) displayed significantly more Slow-Wave Sleep (SWS). Although the results are suggestive of an effect of 5-HTTLPR on expression of sleep states, it is difficult to draw firm conclusions, because of the small number of participants. As discussed earlier, the 's' allele results in decreased re-uptake of serotonin, thus allowing for higher levels of serotonin availability. The finding of increased SWS in individuals with the 's' allele is consistent with data from pharmacologically manipulated serotonin studies in humans (Linn, et al., 2007).

Benedetti and colleagues (Benedetti et al., 1999) examined the influence of 5-HTTLPR on total sleep deprivation in individuals with bipolar depression. The hypothesis of the study, that 5-HTTLPR is differentially associated with the effects of total sleep deprivation in bipolar depression was based first on evidence that sleep deprivations in cats enhanced the functioning of the neurotransmitter systems (including 5-HT pathways) and second, evidence from patients' response to serotonergic drugs. Previous research using a bi-allelic classification of 5-HTTLPR (ll, sl vs. ss) reported that individuals homozygous for the 's' allele responded worse to paroxetine and

fluvoxamine compared to individuals with at least one copy of the 'l' allele (ll,sl) (Smeraldi et al., 1998; Zanardi, Benedetti, Di Bella, Catalano, & Smeraldi, 2000). Benedetti et al. examined 68 inpatients meeting criteria for bipolar disorder Type I (depressive episode without psychotic features) and who had been drug free, for a minimum of 7 days. All patients experienced a night of total sleep deprivation followed by a night of undisturbed sleep. Mood was rated using the Hamilton Depression Rating scale for 3 days, 3 times a day on a visual analogue scale ranging from depression (0) to euthymia (50) and euphoria (100). Genotype frequencies were in Hardy-Weinberg equilibrium. The authors report a significant time by group interaction with patients homozygous for the 'l' allele displaying a better mood amelioration following total sleep deprivation compared to those with one copy of the S allele (ss, sl).

Perlis and colleagues (2003) examined whether 5-HTTLPR moderates some SSRI-induced adverse effects including sleep and agitation. There is evidence to suggest that SSRIs are associated with treatment induced adverse effect such as insomnia. Identifying individuals who might be more at risk for treatment of emergent adverse effects is of great interest to researchers. A sample of 36 Caucasians meeting DSM-IV criteria for major depressive disorder was seen weekly for 6 weeks, bi-weekly for 4 weeks and weekly for another 2 weeks. During this period they were administered 10µg/day of fluoxetine for one week, 20 µg/day for the next 3 weeks, 40 µg/day for the following 4 weeks. Dosage was increased to 60µg/day for the remaining weeks if participants were not responding to 40 µg/day. A logistic regression with insomnia as the outcome, genotype as the predictor and depression severity and anxiety somatization factor as covariates indicated that the 'ss' term was the only significant predictor. The same result was obtained when insomnia was substituted for agitation. The authors examined whether this might be the results of individuals homozygous for the 's' allele reporting higher overall on adverse effects due to treatment side-effects such as diarrhea, dizziness, dry mouth, sexual dysfunction, decreased libido, nausea and headaches but found no difference according to genotype for these adverse effects. The authors further report that symptoms of agitation and insomnia were presented earlier in individuals homozygous for the 's' allele compared to the other participants, which would also suggest that they occurred whilst on a smaller dose of fluoxetine. Finally, insomnia and agitation were associated with higher depression scores at the end of treatment for subjects with at least one S allele.

3.1.5.4 *Summary of studies*

This section has considered six studies, which examine either the role of 5-HTTLPR on sleep or an interaction of 5-HTTLPR with an environmental or pharmacological intervention to predict sleep. The studies are different from each other and different from this study and it is therefore difficult to extrapolate. The issue of sample size has received a lot of attention in relation to establishing a main effect or a GxE interaction effect. The sample sizes of the aforementioned studies ranged from $n=36$ (Perlis, et al., 2003) to $n=993$ (Deuschle, et al., 2010) and, even though most studies mention small sample size as a limitation, none report the achieved power. Based on Duncan and Keller, only one of these studies (Deuschle, et al., 2010), has achieved the recommended power of 80% to detect these effects (Duncan & Keller, 2011). Another very important issue not adequately addressed in the above studies is the classification of alleles, distribution of allele frequencies and allele grouping chosen for analysis. None of the studies used a tri-allelic classification. Given the date of publication for some of the studies (Benedetti, et al., 1999) it is possible that tri-allelic classification may not have been available. More importantly, though, several studies fail to mention whether allele distribution was within Hardy-Weinberg equilibrium. Finally, the studies above seem to follow different rules in identifying the groupings as either those with at least one 's' allele (sl+ss) or those with two 's' alleles (ss). Some studies seem to switch groupings between different parts of the analysis (Perlis, et al., 2003).

Two points need to be considered regarding sleep as an outcome. First, the different groups studied and second, the different methodology used for the assessment of sleep. Addressing the first issue, three studies examined sleep in healthy individuals (Barclay, et al., 2011; Brummett, et al., 2007; Linn, et al., 2007) and the remaining studies examined sleep in individuals with depression (Perlis, et al., 2003), bipolar depression (Benedetti, et al., 1999) and insomnia (Deuschle, et al., 2010). Regarding the measurement of sleep some studies used questionnaires, which may be subject to reporter bias, and some used PSG.

Finally, the results suggest that in terms of GxE interaction, carriers of the 's' allele, under stressful conditions such as caring for an individual with Alzheimer's report worse sleep (Brummett, et al., 2007), and those with bipolar depression, will show a smaller increase in mood compared to carriers of the 'l' allele following total sleep deprivation (Benedetti, et al., 1999). In terms of main effects of 5-HTTLPR on sleep,

Linn et al. reported more SWS in carriers of the 's' allele (ss,sl); Deuschle et al. reported an over-representation of 's' carriers in the insomnia group; however, Barclay et al. reported poorer sleep quality among those homozygous for the L allele (Barclay, et al., 2011; Deuschle, et al., 2010; Linn, et al., 2007). The final study, by Perlis et al. (2003), reported carriers of the 's' allele showing symptoms of insomnia following administration of SSRIs earlier than other groups, which could not be explained by over-reporting of symptoms from 's' carriers and which was associated with higher scores on depression following SSRI treatment.

In conclusion, the mixed findings and the substantial variations in methodological design make it difficult to draw firm conclusions about the role of 5-HTTLPR in the regulation of sleep.

3.1.6 Antenatal depression and 5-HTTLPR

Despite the wealth of studies examining 5-HTTLPR as a moderator of environmental stressors and later development, only three were identified which examined antenatal mental health specifically as a stressor (Braithwaite et al., 2013; Oberlander, et al., 2010; Pluess, Velders, et al., 2010); none examined infant sleep as an outcome.

Pluess and colleagues (2010) examined whether 5-HTTLPR moderated the association between antenatal anxiety and infant negative emotionality measured at 6 months of age. In a sample of 1,513 infants, from the Generation R cohort, the authors reported that 5-HTTLPR did moderate this association. The results indicated that for carriers of at least one copy of the s allele (only bi-allelic classification was available) greater antenatal anxiety predicted higher negative emotionality. Oberlander and colleagues (2010) investigated the effect of Selective Serotonin Re-uptake Inhibitors (SSRIs) on child behaviour at 3 years of age. The authors hypothesised that infants homozygous for the short allele (ss) would be at increased risk of behavioural disturbances compared to the other two groups (sl, ll). In a group of 75 infants (33 had depressed mothers who had been treated with SSRIs during pregnancy and 42 had non-SSRI treated mothers) the authors reported that, in infants homozygous for the short allele, the association between high antenatal maternal anxiety and anxious/depressive symptoms was stronger. However, the association between antenatal maternal anxiety and externalizing behaviour was strongest in infants homozygous for the l allele. Although

the study does provide some evidence that 5-HTTLPR does moderate the association between antenatal depression and child behaviour, the results must be interpreted with caution as the evidence was inconsistent across outcomes and the sample size was small.

Finally, Braithwaite and colleagues²⁵ (2013) investigated whether 5-HTTLPR moderated the association between antenatal anxiety and child behaviour, assessed as infant temperament at 6 months and emotional and behavioural problems from 4-13 years of age. The analysis, using a large sample who were part of the ALSPAC cohort (n=3946), revealed that 5-HTTLPR did not act as a moderator of this association.

The contrasting findings amongst these three studies highlight, first the need for large samples to reliably examine GxE effects and, second, that the role of the serotonin transporter gene in moderating the effects of antenatal stress is not as straightforward as previously thought.

3.1.7 The Bright Side - The Theory of differential susceptibility in GxE research

The focus of the overwhelming majority of GxE studies has been to identify the individuals more at risk of developing maladaptive behaviours or at risk of developing depression. In the case of 5-HTTLPR, studies have in general supported that those homozygous for the 's' allele are more at risk. Murrough and Charney (2011, p. 511) argue that this is evidence for a *'heightened neural and endocrine response to stress which acts as a stable phenotype elevating an individual's risk'*.

In the previous chapter the theory of differential susceptibility was discussed which posits that the same individuals more at risk for developing maladaptive behaviours when exposed to stressful conditions will be more likely to thrive under protective and supportive environments. Homberg and Lesch (2010, p. 513) argue that, in evolutionary terms, it is unlikely that a *"disease-associated polymorphism"*, which would only confer risk for psychopathology, would have survived. They argue that a plausible explanation is that these *"fundamentally neutral common genetic factors are shaped by the environment and may lead to negative outcomes, although they maintain the potential for positive behavioural manifestations"*. It seems logical, therefore, to examine whether the same polymorphism would, under certain conditions such as a supportive

²⁵ Co-author on this work.

and positive environment or the absence of parental mental health problems, be associated with positive development.

Most of the evidence regarding 5-HTTLPR is in line with a diathesis stress model although there is some evidence to suggest that known risk genes such as 5-HTTLPR or DRD4 might also act as plasticity genes. Under adversity these genes confer increased risk for negative outcomes whereas under supportive and enriched environments they confer positive development (Belsky, et al., 2009).

A recent meta-analysis by van IJzendoorn and colleagues (2012) examined whether 5-HTTLPR acted as a marker of differential susceptibility in child and adolescent GxE studies. When the complete sample was used for analysis, the authors reported carriers of at least one 's' allele (ss/sl) to be more negatively affected by adverse contexts compared to individuals homozygous for the 'l' allele; but they did not find them to benefit significantly more in positive environment. They also found ethnicity to be a moderator of this association. The analysis was repeated with samples using Caucasian (or mostly Caucasian) individuals. Carriers of at least one copy of the s allele were found to be disproportionately affected by negative environments compared to individuals homozygous for the 'l' allele, but also to benefit more from supportive environments. This finding gives therefore, some support to the role of 5-HTTLPR as a marker of differential susceptibility.

3.1.8 Rationale

There is evidence suggesting that antenatal depression predicts infant sleep (see section 1.3); indeed this association has already been established in the ALSPAC study (O'Connor, 2007). Understanding the development of sleep and sleep disturbances, and more importantly, identifying who may be more at risk for sleep disturbances when exposed to environmental stressors, such as antenatal depression, is necessary when targeting interventions.

A number of studies have investigated whether GxE interactions can help identify those more at risk. Serotonin is a key neurotransmitter in the regulation of sleep-wake cycle and studies which have assessed the serotonin transporter gene 5-HTTLPR suggest that carriers of the s allele, when exposed to adversities early in life such as abuse and maltreatment, are more at risk for depression during adulthood. It is therefore an ideal candidate gene to study in this context.

This is the first study to examine whether 5-HTTLPR acts as a moderator of the association between antenatal depression and infant sleep.

3.1.9 Aims and Hypotheses

The overall aim of this study was to examine whether the association of antenatal depression and infant sleep is moderated by a polymorphism of the serotonin transporter promoter gene area (5-HTTLPR) in two population cohort studies. It was hypothesized that the association between maternal antenatal depression and infant sleep would be stronger in those infants with low activity alleles of the serotonin transporter promoter polymorphism (5-HTTLPR) compared to those with high activity alleles²⁶. More specifically it was hypothesized that infants carrying the low activity alleles would exhibit:

- i. shorter sleep duration ,
- ii. a higher number of awakenings,
- iii. and a higher number of sleep problems when exposed to maternal antenatal depression.

²⁶ For ALSPAC triallelic classification available (SS, SL_G, L_GL_G vs. L_AL_A)

For Generation R biallelic classification available (SS vs. LL)

3.2 STUDY I - THE AVON LONGITUDINAL STUDY OF PARENTS AND CHILDREN (ALSPAC)

3.2.1 Methods

3.2.1.1 *Setting and Procedure*

A detailed description of the ALSPAC cohort can be found in Section 2.2.1.1, page 75. Genetic data was available for a subsample of the ALSPAC cohort, $n=5,409$. The sample was then limited to Caucasian participants as research suggests that 5-HTTLPR may function differently across ethnic groups. Figure 5, illustrates missing data at each level, leading to the number of participants used for this analysis at 6 months ($n=4,440$).

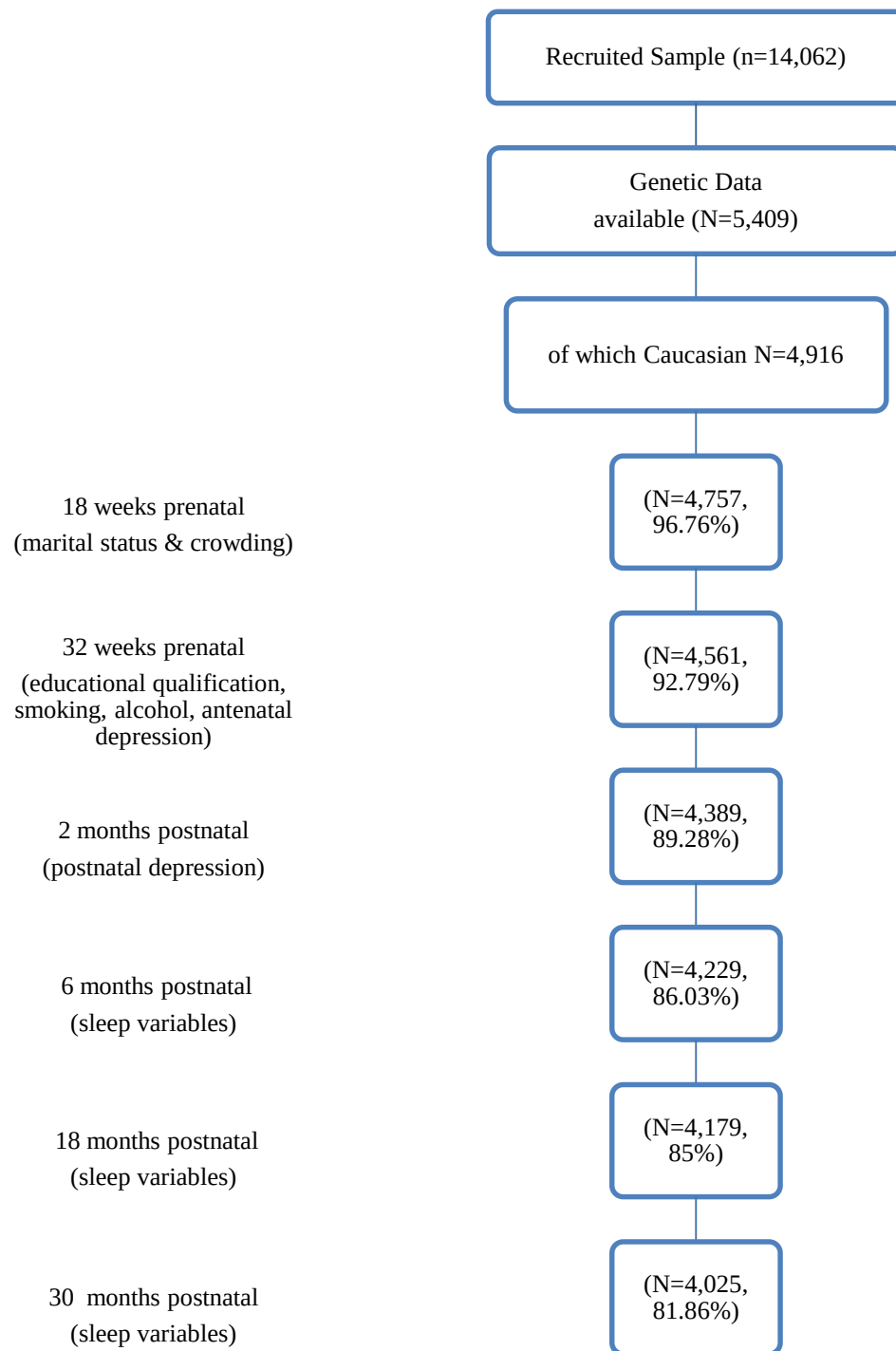


Figure 11: Flowchart to display data attrition for genetic data analysis in the ALSPAC cohort.

3.2.1.2 *Participants*

Demographic characteristics of the sample used for this analysis are presented in Table 21.

A comparison between the sub-sample included and the whole ALSPAC sample revealed that in this group of participants:

- a. There was a higher proportion of married women;
- b. Women had higher educational qualification;
- c. There was a higher proportion of boys;
- d. A lower number of people living in the household;
- e. Women were slightly older compared to the total sample;
- f. There was a higher proportion of women who did not smoke;
- g. Women had lower scores of antenatal and postnatal depression;
- h. There were no differences in terms of alcohol consumption.

Differences were also examined for infant sleep between the whole ALSPAC sample and the sub-sample included in this analysis. Differences were evident for sleep duration at 6 months, night awakenings at 18 months and sleep problems at 18 and 30 months with the sub-sample of children included in this analysis having longer sleep duration at 6 months, fewer awakenings at 18 months and fewer sleep problems at 18 and 30 months²⁷. No differences were evident for night awakenings at 6 or 30 months of age or for sleep duration at 18 or 30 months of age²⁸.

²⁷ For sub-sample vs. remaining sample for sleep duration at 6 months mean=12:87 SE=0.03 vs mean=12:75 SE=0.03, $t(11008)=-2.7$, $p=.007$, awakenings at 18 months mean=0.78, SE=0.02 vs mean=0.83 SE=0.01, $t(10859)=2.15$, $p=.107$, for sleep problems at 18 months mean=2.1, SE=0.03 vs mean=2.35 SE=0.02, $t(11033)=7.17$, $p<.001$, for sleep problems at 30 months mean=3.01, SE=0.03 vs mean=3.2 SE=0.03, $t(9871)=4.65$, $p<.001$

²⁸ Subsample vs. remaining sample for awakenings at 6 months mean=0.58 SE=0.02 vs mean=0.56 SE=0.2, $t(11356)=-.90$, $p=.371$, at 30 months, mean=0.74 SE=0.02 vs mean=0.77 SE=0.2, $t(10157)=1.18$, $p=.24$, sleep duration at 18 months, mean=11:35 SE=0.01 vs mean=11:31 SE=0.1, $t(10876)=-1.61$, $p=.107$, at 30 months, mean=12:45 SE=0.0 vs mean=12:45 SE=0.0, $t(10056)=-.032$, $p=.975$

Table 21: Comparison of demographic characteristics of the current sample (n=5,409) and the whole ALSPAC sample (n=14,062)

Variables	Sample with Genetic Data (n=5,084)	Overall ALSPAC sample (n=14,062)	Test Statistic
<u>Maternal characteristics</u>	(%)	(%)	
Marital Status			
Never married	14.4	19.1	$\chi^2(5)=160.025$, p<.001
Widowed	.1	.1	
Divorced	3.5	4.3	
Separated	1.3	1.6	
1st marriage	74.2	68.4	
Marriage 2 or 3	6.5	6.5	
Educational Qualification			
CSE	13.5	20.2	$\chi^2(4)=352.184$, p<.001
Vocational	8.8	9.8	
O level	35.2	34.6	
A level	26.1	22.5	
Degree	16.4	12.9	
Smoking			
0	85.3	80.1	$\chi^2(3)=153.67$, p<.001
1-9	6.2	7.7	
10-19	6.4	9.1	
20+	2.1	3.2	
Alcohol	mean=1.74, SD=3.58 range(1-36)	mean=1.67, SD=3.71, range(0-65)	t(6922)=-1.476, p=.14
Maternal Age	mean=29.04, SD=4.65, range(15-44)	mean=28, SD=4.97, range(15-44)	t(14080)=-20.029, p<.001
Crowding	mean=1.59, SD=.62, range(1-4)	mean=1.67, SD=.66, range(1-4)	t(13230)=11.986, p <.001
Ethnic Background:			
White	100	97.4	
Maternal measures			
Depression at 32 weeks gestation	mean=6.66, SD=4.84, range(0-29)	mean=7.08, SD=5.08, range(0-29)	U(1)=19.25, p<.001
Depression 2 months postpartum	mean=5.84, SD=4.93, range(0-28)	mean=6.21, SD=4.57, range(0-27)	U(1)=16.19, p=.002
<u>Child characteristics</u>			
Child Sex			
Male	52.9	51.7	$\chi^2(1)=4.494$, p=.034

3.2.1.3 Measures

Antenatal depression was measured at 32 weeks gestation, postnatal depression was measured at 8 weeks postnatally and infant sleep was measured at 6, 18, and 30 months of age. A number of demographic characteristics were assessed and included in the analysis. Crowding and marital status were assessed at 18 weeks gestation. Maternal smoking, alcohol and educational qualification were assessed at 32 weeks gestation. Information was also collected on maternal age and infant gender. Demographic characteristics were included as covariates if they were associated with antenatal depression, any of the sleep variables or 5-HTTLPR.

3.2.1.3.1 Maternal Depression

Maternal depression was assessed using the Edinburgh Postnatal Depression Scale (EPDS). The measure was described in detail in section 2.2.1.3.1.

3.2.1.3.2 Infant Sleep

Details of the measures and how they were calculated were presented in section 2.2.1.3.3. For this, as with the previous analysis, data from 3 time points were used 6, 18 and 30 months of age.

3.2.1.3.3 Genotyping

DNA was extracted and processed from cord or peripheral blood. A detailed procedure of the DNA extraction and analysis has been previously described (Araya et al., 2009; Barnett, Xu, Heron, Goldman, & Jones, 2010; Jones et al., 2000). It has been demonstrated that the 5-HTTLPR is functionally triallelic (Hu et al., 2006). The six genotypes were grouped by expression level:

- Low activity level: SS, SL_G, L_GL_G
- Medium activity level: SL_A, L_GL_A
- High activity level: L_AL_A

The distribution of the 5-HTTLPR triallelic genotype was: SS (16.6%), SL_G(6%), L_GL_G(.8%), SL_A(44.1%), L_GL_A(7.1%), L_AL_A(25.4%). The distribution is similar to that of other Caucasian populations (Hu, et al., 2006) and similar to studies which have previously used this cohort (Araya, et al., 2009). Using the three activity groupings and the six allelic groupings the data were in Hardy –Weinberg equilibrium ($\chi^2=3.39$, $p=.49$, $\chi^2=13.56$, $p=.42$).

3.2.1.3.4 Covariates

Similarly to the analysis presented in Chapter 2, a number of covariates were included in the analysis: marital status, crowding, maternal age, maternal smoking, alcohol consumption, educational qualification and postnatal depression assessed at 2 months postpartum.

3.2.1.4 Analysis Plan

The analysis was undertaken in four stages:

First, descriptive analyses of antenatal maternal depression, the 5-HTTLPR alleles, and the sleep variables were undertaken. Analysis of Variance (ANOVA) tests were then used to examine differences in sleep variables according to genotype.

Second, inter-correlations of sleep variables were examined. At this stage associations between sleep variables and 5-HTTLPR, depression and demographic characteristics were also examined using Pearson correlations.

Third, the moderator analysis was undertaken. This is presented by time point during which sleep data were collected: 6 months, 18 months and 30 months. Hierarchical linear regression models were constructed with gender and covariates included in the first step; antenatal depression and 5-HTTLPR in Step 2; three 2-way interactions in Step 3 (antenatal depression x 5-HTTLPR, antenatal depression x gender, 5-HTTLPR x gender); and a 3-way interaction in Step 4 (antenatal depression x 5-HTTLPR x gender).

All variables used for interaction models were centered to overcome problems of multicollinearity (Aiken, et al., 1991).

3.2.2 Results

3.2.2.1 Treating Data

As was previously discussed in 2.2.2.1, the sleep variables and antenatal depression were not normally distributed. The procedures outlined earlier were also followed here to deal with outliers and distribution issues.

3.2.2.2 Descriptive Statistics

Analysis presented here is limited to participants with complete genetic data. Descriptive statistics for antenatal depression²⁹ and frequencies and percentages for 5-HTTLPR are presented in Table 22. Antenatal depression was not associated with 5-HTTLPR $r=.02$, $p=.196$.

Table 22: Descriptive statistics for antenatal depression and Genotype frequencies for 5-HTTLPR including the A/G SNP ($n=5,084$).

	Mean	SD	Range	Median
Antenatal depression	6.73	4.88	0-29	6.00

5-HTTLPR	Frequency (%)
Low expression(SS, SL_G, L_GL_G)	1187 (23.3)
Medium expression(SL_A, L_GL_A)	2595 (51)
High expression(L_AL_A)	1302 (25.6)
Total	5084 (100)

Descriptive statistics for sleep variables are presented by genotype and by gender in Tables 23-25 and by time point. There was no significant effect of genotype on infant sleep³⁰. Differences in sleep were also examined. Boys slept longer at 30 months of age,

²⁹ A Kolmogorov-Smirnov test was performed and the data were found to be non-normally distributed, $D(5079)=.096$, $p<.001$.

³⁰ There was no significant effect of genotype on total sleep time $F(2, 4831)=.514$, $p=.598$ and number of awakenings $F(2,4831)=1.082$, $p=.339$ at 6 months of age. There was also no significant effect of genotype on sleep variables for total sleep time $F(2,4893)=.525$, $p=.592$, number of awakenings $F(2,4899)=1.581$, $p=.206$ or sleep problems $F(2,4962)=.143$ $p=.867$ at 18

had more awakenings at 6 and 30 months and more sleep problems at 30 months³¹. Girls slept longer than boys at 6 and 18 months of age³². There were no differences in awakenings and sleep problems at 18 months³³.

months of age or for total sleep time $F(2,4487)=.05$, $p=.951$, number of awakenings $F(2, 4487)=.746$, $p=.475$ or sleep problems $F(2, 4487)=.015$, $p=.985$ at 30 months of age.

³¹ 30month sleep duration, $t(4712)=6.23$, $p<.001$, 6 month awakenings: $t(4994)=5.43$, $p<.001$,

³² 6 month sleep duration $t(4854)=2.31$, $p=.021$, 18 month sleep duration $t(4894)=2.79$, $p=.005$, 30 month awakenings $t(4746)=2.29$, $p=.022$, 30 month problems $t(4307)=2.48$, $p=.013$

³³ 18 month awakenings $t(4900)=1.75$, $p=.08$, sleep problems $t(4601)=1.45$, $p=.15$

Table 23: Descriptive statistics for total sleep time and awakenings by genotype and gender at 6 months of age

	Boys				Girls				Total			
	N	Mean (hh:mm)	SD	Range	N	Mean (hh:mm)	SD	Range	N	Mean (hh:mm)	SD	Range
Low expression	570	12:47	01:57	6:30-18:00	544	13:00	01:57	6:30-19:30	1114	12:54	01:57	6:30-19:30
Medium expression	1326	12:45	01:58	6:30-19:30	1177	12:54	01:58	5:00-19:00	2503	12:49	02:00	6:30-19:30
High expression	652	12:42	02:04	6:30-19:00	587	12:58	01:50	6:30-19:30	1239	12:49	01:58	6:30-19:30
Total	2548	12:45	02:00	6:30-19:30	2308	12:57	01:56	6:30-19:30	4856	12:51	01:58	6:30-19:30

	Boys				Girls				Total			
	N	Mean	SD	Range	N	Mean	SD	Range	N	Mean	SD	Range
Low expression	599	0.67	1.27	0-5	559	0.48	1.05	0-5	1158	0.58	1.17	0-5
Medium expression	1375	0.63	1.21	0-5	1199	0.47	1.07	0-5	2574	0.56	1.15	0-5
High expression	665	0.68	1.31	0-5	599	0.45	1.10	0-5	1264	0.57	1.22	0-5
Total	2639	0.65	1.25	0-5	2357	0.47	1.07	0-5	4996	0.57	1.17	0-5

Table 24: Descriptive statistics for sleep variables by genotype and by gender at 18 months of age.

Total Sleep Time												
	N	Mean	Boys SD	Range	N	Mean	Girls SD	Range	N	Mean	Total SD	Range
Low expression	594	11:15	01:00	8:00-14:30	548	11:28	01:01	8:00-14:30	1142	11:21	01:01	8:00-14:30
Medium expression	1345	11:16	01:00	8:00-14:30	1159	11:23	01:00	8:00-14:30	2504	11:19	00:59	8:00-14:30
High expression	661	11:16	01:01	8:00-14:30	589	11:23	01:01	8:00-14:30	1250	11:19	01:01	8:00-14:30
Total	2600	11:16	01:00	8:00-14:30	2296	11:24	01:00	8:00-14:30	4896	11:20	01:00	8:00-14:30

No. of awakenings at night												
	N	Mean	Boys SD	Range	N	Mean	Girls SD	Range	N	Mean	Total SD	Range
Low expression	594	0.78	.98	0-5	549	0.80	1.05	0-5	1143	0.79	1.01	0-5
Medium expression	1350	0.79	0.99	0-5	1160	0.70	0.96	0-5	2510	0.75	0.98	0-5
High expression	660	0.83	1.08	0-5	589	0.79	1.00	0-5	1249	0.81	1.04	0-5
Total	2604	0.80	1.01	0-5	2298	0.75	.99	0-5	4902	0.77	1.00	0-5

Sleep Problems												
	N	Mean	Boys SD	Range	N	Mean	Girls SD	Range	N	Mean	Total SD	Range
Low expression	550	2.05	1.84	0-7	527	2.13	1.9	0-7	1077	2.08	1.87	0-7
Medium expression	1253	2.15	1.83	0-7	1095	2.06	1.86	0-7	2348	2.11	1.85	0-7
High expression	617	2.23	1.12	0-7	561	2.03	1.86	0-7	1178	2.13	1.89	0-7
Total	2420	2.17	1.87	0-7	2183	2.09	1.88	0-7	4603	2.13	1.87	0-7

Table 25: Descriptive statistics for sleep variables at 30 months by genotype and by gender.

	Boys				Total Sleep Time				Girls				Total			
	N	Mean	SD	Range	N	Mean	SD	Range	N	Mean	SD	Range	N	Mean	SD	Range
Low expression	574	12:30	00:33	10.30-16.30	523	12:24	00:33	9:30-16:00	1097	12:27	00:33	9:30-16:00	1097	12:27	00:33	9:30-16:00
Medium expression	1289	12:30	00:33	10:00-16:00	1114	12:24	00:33	9:30-16:00	2403	12:27	00:33	9:30-16:00	2403	12:27	00:33	9:30-16:00
High expression	642	12:30	00:34	10:00-16:00	572	12:23	00:34	9:30-16:00	1214	12:27	00:34	9:30-16:00	1214	12:27	00:34	9:30-16:00
Total	2505	12:30	00:33	10:00-16:00	2209	12:24	00:33	9:30-16:00	4714	12:27	00:33	9:30-16:00	4714	12:27	00:33	9:30-16:00
Awakenings																
Low expression	579	0.73	0.84	0-4	524	0.74	0.91	0-4	1103	0.73	0.87	0-4	1103	0.73	0.87	0-4
Medium expression	1312	0.77	0.92	0-4	1115	0.67	0.88	0-4	2427	0.72	0.91	0-4	2427	0.72	0.91	0-4
High expression	642	0.77	0.94	0-4	576	0.74	0.91	0-4	1218	0.76	0.92	0-4	1218	0.76	0.92	0-4
Total	2533	0.760	0.9	0-4	2215	0.70	0.897	0-4	4748	0.73	0.90	0-4	4748	0.73	0.90	0-4
Sleep Problems																
Low expression	524	3.07	1.9	0-7	481	2.96	1.93	0-7	1005	3.01	1.92	0-7	1005	3.01	1.92	0-7
Medium expression	1179	3.03	1.97	0-7	1015	2.9	2.02	0-7	2194	3.01	1.99	0-7	2194	3.01	1.99	0-7
High expression	583	3.1	2	0-7	527	2.9	1.97	0-7	1110	3.01	1.98	0-7	1110	3.01	1.98	0-7
Total	2286	3.1	1.96	0-7	2023	2.95	2	0-7	4309	3.03	1.98	0-7	4309	3.03	1.98	0-7

3.2.2.3 *Correlational analyses of sleep variables*

Correlational analyses were conducted to explore the associations between the sleep variables at all time points for this subset of the ALSPAC cohort. The correlations observed are almost identical to the correlations table presented earlier (Chapter 2 Table 6) in terms of how the sleep variables relate to each other. The correlations are discussed here again, as this is a sub-sample of the ALSPAC cohort and the sample size is different to the one presented earlier. All variables were correlated to each other showing aspects of stability and continuity in the assessment of sleep across time and were in the expected directions. This table can be found in Appendix 13. Sleep problems at 18 months were significantly correlated to sleep problems at 30 months ($r=.442$, $p<.001$). Awakenings at different time points were all positively associated, with coefficients ranging from low ($r=.122$, $p<.001$) for awakenings at 6 months and 30 months to moderate ($r=.455$, $p<.001$) for awakenings at 18 and 30 months. Inter-correlations of total sleep time were not in the expected direction with sleep time at 30 months negatively associated with total sleep at 6 ($r=-.269$, $p<.001$) and 18 months ($r=-.528$, $p<.001$).

Bivariate correlations for depression, sleep variables, genotype and socio-demographic characteristics were examined by time point and are presented in the Appendices, again by time point.

Significant correlations of small magnitude were found for antenatal depression and all socio-demographic characteristics and a correlation of medium magnitude for antenatal and postnatal depression ($r=.57$, $p<.001$). Correlations of small magnitude were found for antenatal depression and 5-HTTLPR in the sub-samples at 18 and 30 months of age (Appendix 15 and Appendix 16). Following adjustment for multiple testing, after which the association did not hold, and given the small coefficients, these associations were not further explored. No associations were found for 5-HTTLPR and any of the covariates.

3.2.2.3.1 **At 6 months**

Maternal antenatal depressive symptoms were not associated with infant total sleep time ($r=-.006$, $p=.672$) or number of awakenings ($r=.016$, $p=.303$) at 6 months. The two sleep variables were negatively associated with each other ($r=-.242$, $p<.001$ - Appendix 14).

3.2.2.3.2 At 18 months

At 18 months of age there were two significant correlations of small magnitude between antenatal depression and i) awakenings ($r=.054$, $p<.001$), and ii) sleep problems ($r=.138$, $p<.001$ - Appendix 15).

3.2.2.3.3 At 30 months

Antenatal depression was significantly associated with sleep problems at 30 months of age ($r=.149$, $p<.001$ - Appendix 16). Crowding was associated with all sleep variables. Total sleep time and sleep problems were also associated with marital status and smoking. Finally, number of awakenings was associated with education ($r=-.065$, $p<.001$) and postnatal depression ($r=.034$, $p=.02$).

3.2.2.4 Moderator analysis

3.2.2.4.1 Sleep at 6 months of age: Does 5-HTTLPR moderate the association between antenatal depression and infant sleep at 6 months of age (sleep duration and awakenings)?

Two hierarchical linear regressions were conducted to assess whether the polymorphism of the serotonin transporter promoter (5-HTTLPR) would interact with antenatal depression to predict a) total sleep time and b) awakenings at 6 months of age. The results of these analyses are presented in Table 26.

Total sleep duration

The steps of the analysis were undertaken as described in section 2.2.1.4. There was no evidence of a moderating effect ($\beta=.040$, $p=.399$) for sleep duration at 6 months of age.

Number of nighttime awakenings

There was no evidence of a moderating effect for awakenings at 6 months of age ($\beta=-.064$, $p=.166$).

Table 26: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on the association between antenatal depression and a) sleep time and b) number of awakenings at 6 months, Step 4.

	Sleep at 6 months		Awakenings 6 months	
Variables	β	p	β	p
Step 1				
Postnatal Depression	-.054	.004	.005	.774
Gender	.044	.341	-.090	.048
Ed. Qualification	.020	.223	.072	.000
Alcohol	.006	.673	-.018	.245
Smoking	.031	.057	-.025	.114
Crowding	.035	.026	.035	.025
Marital Status	.056	.000	-.016	.317
Maternal Age	-.081	.000	.061	.000
Step 2				
Antenatal Depression	.073	.130	-.025	.597
5-HTTLPR	-.015	.309	-.01	.515
Step 3				
5-HTTLPR x Gender	.000	.999	.020	.663
Depression x 5-HTTLPR	-.054	.250	.053	.256
Depression x Gender	-.037	.428	.078	.095
Step 4				
Depression x 5-HTTLPR x Gender	.040	.399	-.064	.166
	R ² =.019 F(14,4114)=4.395,p<.001 n=4,119		R ² =.019 F(14,4214)=6.062,p<.001 n=4,229	

3.2.2.4.2 Sleep at 18 months of age: Does 5-HTTLPR moderate the association between antenatal depression and infant sleep at 18 months of age (total sleep time, awakenings and sleep problems)?

There was no evidence to suggest that 5-HTTLPR and gender moderated the association between antenatal depression and any of the infant sleep variables at 18 months. The complete regression models can be found in pages 299-301.

Table 27: Summary of Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on the association between antenatal depression and a) total sleep time, b) awakenings and c) sleep problems at 18 months, Step 4.

	Sleep Duration		Awakenings		Sleep Problems	
Variables						
Step 1	β	p	β	p	β	p
Postnatal Depression	-.008	.650	.039	.036	.064	.000
Gender	.116	.011	.019	.676	.042	.358
Ed. Qualification	.058	.000	-.082	.000	-.111	.000
Alcohol	.029	.058	-.043	.005	-.010	.502
Smoking	.061	.000	-.019	.247	-.013	.400
Crowding	.004	.801	.045	.005	.018	.247
Marital Status	.032	.043	.007	.675	-.027	.078
Maternal Age	-.144	.000	.048	.003	-.035	.025
Step 2						
Antenatal Depression	-.042	.380	.023	.631	.095	.046
5-HTTLPR	-.012	.424	.015	.306	.001	.925
Step 3						
5-HTTLPR x Gender	-.057	.213	-.029	.523	-.063	.165
Depression x 5-HTTLPR	.013	.781	.003	.948	-.003	.949
Depression x Gender	-.070	.135	.073	.119	.028	.546
Step 4						
Depression x 5-HTTLPR x Gender	.066	.158	-.063	.183	-.014	.767
	R ² =.029		R ² =.017		R ² =.042	
	F(14,4116)=9.206,p<.001		F(14,4118)=5.264,p<.001		F(14,4164)=13.778,p<.001	
	n=4,131		n=4,133		n=4,179	

3.2.2.4.3 Sleep at 30 months of age: Does 5-HTTLPR moderate the association of antenatal depression and infant sleep at 30 months of age (total sleep time and awakenings and sleep problems)?

There was no evidence to suggest the 5-HTTLPR and gender moderated the association between antenatal depression and any of the infant sleep variables at 30 months of age. The complete regression models can be found in pages 302-304.

Table 28: Summary of Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR on antenatal depression and a) sleep duration, b) awakenings and c) sleep problems at 30 months of age, Step 4.

	Sleep Duration		Awakenings		Sleep Problems	
Variables						
Step 1	β	p	β	p	β	P
Postnatal Depression	-.110	.018	.017	.354	.078	.000
Gender	-.037	.026	.003	.955	-.012	.794
Ed. Qualification	.041	.009	-.062	.000	-.097	.000
Alcohol	-.030	.061	.004	.797	.008	.585
Smoking	-.023	.150	-.003	.847	.024	.146
Crowding	-.007	.677	.021	.192	-.007	.647
Marital Status	.154	.000	.006	.696	-.006	.714
Maternal Age	.147	.000	.028	.088	-.051	.002
Step 2						
Antenatal Depression	-.008	.867	.007	.879	.156	.001
5-HTTLPR	.003	.848	.006	.674	-.010	.515
Step 3						
5-HTTLPR x Gender	.022	.632	-.026	.584	-.030	.524
Depression x 5-HTTLPR	.014	.764	.010	.838	-.065	.172
Depression x Gender	.071	.131	.067	.160	-.023	.632
Step 4						
Depression x 5-HTTLPR x Gender	-.054	.252	-.070	.144	.038	.418
	R ² =.036		R ² =.007		R ² =.046	
	F(14,3985)=11.235,p<.001		F(14,4010)=2.204,p=.006		F(14,3918)=14.278,p<.001	
	n=4,000		n=4,025		n=3,933	

Summary of Findings

There was no evidence that 5-HTTLPR acted as a moderator of the association between antenatal depression and infant sleep at 6, 18 or 30 months for the sleep variables examined here (sleep duration, number of night awakenings, sleep problems).

3.3 STUDY II - GENERATION R

3.3.1 Methods

3.3.1.1 Participants

The Generation R cohort was described in detail in the previous chapter (section 2.3.1.1). The analysis here is performed on an ethnically homogeneous sample, including only Caucasian participants for whom genetic data were available. The analysis here follows as closely as possible the analysis presented in Study I. Figure 12 depicts the attrition of data. The Caucasian participants for whom genetic data were available were compared to the remaining Generation R cohort for differences in demographic characteristics. Analysis indicated the following differences between those two groups:

Those families for whom data were available for this analysis had mothers who:

- a. Were slightly older;
- b. Had lower scores on the depression scale during pregnancy;
- c. Were more likely to have a university degree;
- d. Consumed more alcohol during pregnancy;
- e. Were more likely to be married;
- f. Lived with fewer people in the household;
- g. No differences were found for smoking during pregnancy and gender between the two groups;

Differences in sleep variables revealed that included children slept more both during 6 months³⁴ and 24 months of age. In terms of awakenings, at both 6 and 24 months of age participants with available data had fewer number of awakenings compared to those for whom genetic data was not available³⁵.

³⁴ 6 months: Mean=10:48 SE=00:02 vs. Mean=10:30, SE= 00:02 ,t(4068)=-6.24, p<.001

24 months: Mean=11:06 SE=00:01 vs. Mean=10:51, SE= 00:01, t(5058)=-9.07, p<.001

³⁵ at 6 months $\chi^2(3)=14.16$, p=.003, at 24 months $\chi^2(3)=25.23$, p<.001

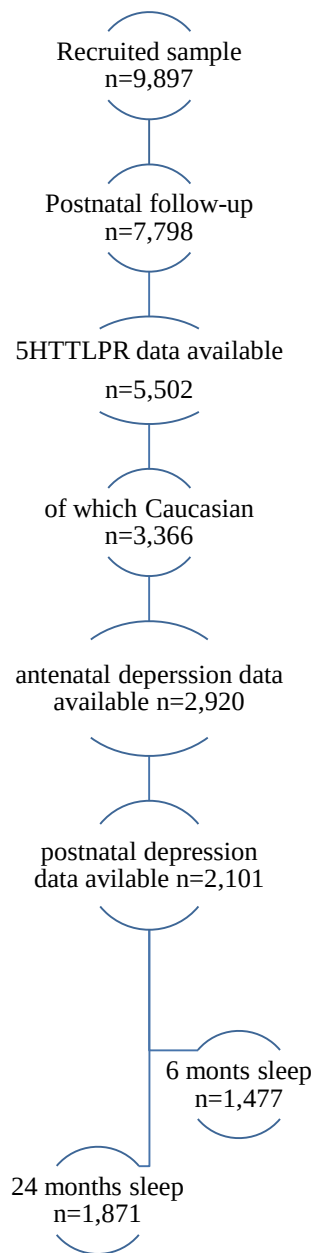


Figure 12: Flowchart to illustrate attrition of genetic data in the Generation R cohort.

Table 29: Comparison of demographic characteristics of sub-sample with genetic data available with total Generation R sample.

Generation R			
	Sample for this study n=3,366 (%)	Overall Generation R Sample n=7,795 (%)	Test Statistic
<u>Variables</u>			
<u>Maternal characteristics</u>			
Marital Status			
Married/Living with Partner	91.3	87.3	$\chi^2(1)=140.4, p<.001$
Without partner	8.7	12.7	
Educational Qualification			
Secondary	67.6	73.2	$\chi^2(5)=540.14, p<.001$
Degree	32.4	26.5	
Smoking during Pregnancy			
Yes	27.1	25.6	$\chi^2(1)=.027, p=.870$
Alcohol during Pregnancy			
Yes	67	55.7	$\chi^2(1)=487.34, p<.001$
Age of mother (yrs)	mean=31.59, SD=4.22 (17.12-43.18)	mean=30.41, SD=5.2 (15.27-46.34)	$t(9776)=-12.63, p<.001$
Crowding	mean =2.53 SD=.81	mean=2.64, SD=1.01	$t(6844)=5.57, p<.001$
Ethnic Group			
White	100	66.2	
Depression during pregnancy	mean=.12, SD=.3	mean=.23, SD=.48	$t(6710)=14.13, p<.001$
Depression 2 months postnatal	mean=.16, SD=.35	mean=.22, SD=.46	
<u>Child characteristics</u>			
Child Sex			
Male	1706 (50.7)	3887 (50.5)	$\chi^2(1)=.017, p=.897$

3.3.1.2 Measures

3.3.1.2.1 Maternal Depression

Maternal depression during the antenatal and postnatal periods was assessed using the Brief Symptom Inventory (Derogatis & Melisaratos, 1983). The measure was described in detail in the previous chapter (section 2.3.1.3.1).

3.3.1.2.2 Infant Sleep

Infant sleep was assessed at 6 and 24 months of age and consists of sleep duration and number of night awakenings. Detailed description of the measures and how the variables were calculated can be found in section 2.3.1.3.3.

3.3.1.2.3 Genotyping

DNA was collected from cord blood samples at birth. A detailed description of DNA extraction can be found in (Luijk et al., 2011). Genetic data were available for $n=5,502$ but analysis here is limited to Caucasian participants $n=3,366$. Only biallelic classification of 5-HTTLPR was available in Generation R. Participants were grouped based on whether they were homozygous for the short allele (SS-18.1%), the long allele (LL-33.5%) or heterozygous (SL-48.4%). The data were found to be in Hardy-Weinberg equilibrium³⁶ when using the 3 groupings $\chi^2(1)=.25$, $p=.58$.

3.3.1.2.4 Covariates

A number of covariates were included in the analysis including maternal smoking and alcohol consumption during pregnancy, marital status, educational qualification, crowding and postnatal depression. The measures have already been described in detail (section 2.3.1.3.4).

3.3.1.3 Analysis Plan

The analysis here follows the steps outlined for the analysis carried out in the ALSPAC sample previously.

First, the descriptive statistics for antenatal depression and frequencies of 5-HTTLPR genotype distribution were examined, followed by those for sleep duration and awakenings at 6 and 24 months of age.

³⁶ The calculations were based on (Rodriguez, Gaunt, & Day, 2009).

Second, the correlations for sleep items, depression scores and covariates were examined.

The moderator analysis was the third step of the analysis carried out. Four hierarchical regression analyses were constructed for sleep duration and awakenings at 6 and 24 months of age. The regression models included 4 Steps: Step 1 included all the covariates as well as child gender; Step 2 included antenatal depression and the genotype 5-HTTLPR; in Step 3 the three 2-way interaction terms were added (depression X 5-HTTLPR, antenatal depression X gender, 5-HTTLPR X gender); and in Step 4 the 3-way interaction was added (antenatal depression X 5-HTTLPR X gender).

3.3.2 Results

3.3.2.1 Treating the Data

The procedures outlined in section 2.3.2.1 were also followed here to deal with outliers and distribution issues.

3.3.2.2 Descriptive statistics

Descriptive statistics for antenatal depression and frequencies for 5-HTTLPR are presented in Table 30. Antenatal depression was not associated with 5-HTTLPR $r=.011$, $p=.539$.

Table 30: Descriptive statistics for antenatal depression and Genotype frequencies for 5-HTTLPR, $n=3,366$.

	Mean	SD	Range	Median
Antenatal depression	0.16	0.38	0-3.67	0.0
5-HTTLPR		Frequency (%)		
LL		1127(33.5)		
SL		1629(48.4)		
SS		610(18.1)		
Total		3366(100)		

Descriptive statistics for sleep scores are presented below by gender and by genotype in Tables 31-32. No differences were found for sleep by genotype³⁷. At 6 months there were no differences in sleep duration and awakenings by gender³⁸. At 24 months, boys and girls were significantly different in sleep duration and awakenings, with girls sleeping slightly longer and having fewer awakenings³⁹.

³⁷No significant effect of genotype was found for sleep at 6 months of age for sleep duration $F(2, 1860)=.757$, $p=.469$ or at 24 months, $F(2,2350)=.313$, $p=.731$. There were also no significant differences in the number of night awakenings according to genotype at 6 months of age $\chi^2(6)=5.02$, $p=.541$ or at 24 months of age $\chi^2(6)=7.01$, $p=.320$.

³⁸ 6 months: sleep duration: $t(1859)=.12$, $p=.91$, awakenings: $\chi^2(3)=2.38$, $p=.498$

³⁹ 24 months: sleep duration: $t(2349)=2.82$, $p=.004$, awakenings: $\chi^2(3)=14.15$, $p=.003$.

Table 31: Descriptive statistics for infant sleep at 6 months of age by genotype and by gender.

Sleep Duration												
Boys					Girls				Total			
	Mean	SD	Range	N	Mean	SD	Range	N	Mean	SD	Range	N
LL	10:48	01:28	6:30-14:00	310	10:47	01:42	5:30-14:00	305	10:48	01:34	5:30-14:00	615
SL	10:46	01:25	7:00-15:00	462	10:44	01:39	6:00-14:00	443	10:45	01:32	06:15:00	905
SS	10:50	01:32	8:00-15:00	169	10:55	01:18	7:15-13:45	172	10:52	01:25	07:15-15:00	341
Total	10:48	02:27	6:30-15:00	941	10:47	01:36	05:30-14:00	920	10:48	01:31	5:3015:00	1861

Awakenings										
n(%)										
Boys				Girls			Total			
	SS	SL	LL	SS	SL	LL	SS	SL	LL	Total
0	81 (48.5)	200(43.6)	140(46.2)	86(52.1)	237(54.9)	149(50)	167(50.3)	437(49)	289(48.1)	893
1-2	69(41.3)	211(46)	142(46.9)	67(40.6)	162(37.5)	134(45)	136(41)	373(41.9)	276(45.9)	785
3-4	16(9.6)	35(7.6)	14(4.6)	9(5.5)	32(7.4)	13(4.4)	25(7.5)	67(7.5)	27(2.4)	119
>4	1 (0.6)	13(2.8)	7(2.3)	3(1.8)	1(0.2)	2(0.7)	4(1.2)	14(1.6)	9(0.8)	27
Total	167(100)	459(100)	303(100)	165 (100)	432(100)	298(100)	332(100)	891(100)	601(100)	1824

Table 32: Descriptive statistics of Infant Sleep at 24 months of age by genotype and by gender.

Sleep duration 24 months												
	Boys				Girls				Total			
	Mean	SD	Range	N	Mean	SD	Range	N	Mean	SD	Range	N
LL	11:01	00:52	07:00-13:00	390	11:09	00:50	07:30-14:00	385	11:05	00:51	07:00-14:00	775
SL	11:02	00:52	05:00-1:004	604	11:11	00:50	07:00-13:30	556	11:06	00:51	05:00-14:00	1160
SS	11:10	00:49	08:00-13:00	208	11:04	01:06	03:30-14:00	208	11:07	00:57	03:30-14:00	416
Total	11:03	00:51	05:00-14:00	1202	11:09	00:52	03:30-14:00	1149	11:06	00:52	03:30-14:00	2351

24 month awakenings									
n(%)									
	Boys			Girls			Total		
	SS	SL	LL	SS	SL	LL	SS	SL	LL
0	97(45.5)	269(43.8)	175(43.5)	88(40.9)	267(45.8)	167(41.8)	185(43.2)	536(44.8)	342(42.6)
1-2	110(51.6)	311(50.7)	200(49.8)	113(52.6)	276(47.3)	203(50.7)	223(52.1)	587(49.0)	403(50.2)
3-4	5(2.3)	27(4.4)	23(5.7)	12(5.6)	31(5.3)	24(6.0)	17(4.0)	58(4.8)	47(5.9)
>4	1(0.5)	7(1.1)	4(1.0)	2(0.9)	9(1.5)	6(1.5)	3(0.7)	16(1.3)	10(1.2)
Total	213(100)	614(100)	402(100)	215(100)	583(100)	400(100)	428(100)	1197(100)	802(100)

3.3.2.3 *Correlational analyses*

Correlations were used to examine the associations between sleep variables, antenatal depression and the covariates included in the analysis to follow. The associations here illustrate a similar pattern to the one presented earlier (Chapter 2, Table 17 and Table 18). This analysis can be found in Appendix 25.

Sleep duration and awakenings were negatively associated at 6 and 24 month ($r = -.06$, $p = .013$ and $r = -.15$, $p < .001$) Sleep duration at 6 and 24 months was positively associated as were awakenings at 6 and 24 months ($r = .13$, $p < .001$ and $r = .20$, $p < .001$).

Antenatal depression was negatively associated with sleep duration at 6 months and positively associated with awakenings at 24 months ($r = -.06$, $p = .013$ and $r = .05$, $p = .024$).

5-HTTLPR was not associated with antenatal depression, infant sleep or any of the covariates. Antenatal and postnatal depression were associated with all confounding variables examined besides alcohol consumption.

3.3.2.4 Moderator analysis

3.3.2.4.1 Sleep at 6 months: Does 5-HTTLPR moderate the association between antenatal depression and infant sleep at 6 months of age (sleep duration and night awakenings)?

Two hierarchical linear regression models were conducted to examine whether 5-HTTLPR did moderate the association between antenatal depression and infant sleep.

Step 4 of the results for sleep duration and awakenings is presented in Table 33. There was no evidence that 5-HTTLPR moderated the association between antenatal depression and sleep duration ($\beta=.023$, $p=.458$) or night awakenings ($\beta=-.046$, $p=.130$).

Table 33: Summary of Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on the association between antenatal depression and i) sleep duration, ii) night awakenings. Coefficients for Step 1,2 & 3 are after inclusion of 3-way interaction term in Step 4.

Variables	Sleep Time		Awakenings	
	β	p	β	p
Step 1				
Postnatal Depression	-.001	.983	.063	.058
Gender	.004	.901	.076	.014
Ed. Qualification	-.010	.730	.020	.497
Alcohol	.047	.105	-.035	.231
Smoking	-.002	.940	.098	.001
Crowding	-.018	.539	.072	.012
Marital Status	-.056	.066	.031	.303
Maternal Age	-.063	.055	-.036	.275
Step 2				
Antenatal Depression	.026	.390	-.001	.965
5-HTTLPR	-.012	.706	-.092	.003
Step 3				
Depression x Gender	.000	.999	.005	.859
Depression x 5-HTTLPR	.026	.390	-.042	.165
5-HTTLPR x Gender	.002	.947	.030	.323
Step 4				
Depression x 5-HTTLPR x Gender	.023	.458	-.046	.130
		$R^2=.01$ $F(14,1302)=.904$, $p=.554$	$R^2=.04$	
		$N=1,317$	$F(14,1269)=3.811$, $p<.001$	
			$N=1,284$	

3.3.2.4.2 Sleep at 24 months: Does 5-HTTLPR moderate the association between antenatal depression and infant sleep at 24 months of age (sleep duration and night awakenings)?

A similar model to the one described above was constructed for sleep duration and awakenings at 24 months of age.

Total sleep time

For sleep duration the 3-way interaction term approached significance ($\beta=.048$, $p=.078$). Further exploration by gender revealed that this association was in opposite direction for boys ($\beta=-.050$, $p=.204$) and girls ($\beta=.046$, $p=.247$) but was not found to be significant in either of the two groups⁴⁰.

Night Awakenings

Analysis for awakenings at 24 months of age did reveal significant 3-way interaction ($\beta=-.055$, $p=.035$). Further exploration by gender indicated that the depression X gene interaction term was significant for girls ($\beta=-.093$, $p=.017$) but not for boys ($\beta=.019$, $p=.613$). The regression for girls was further stratified by genotype. The results suggested that for girls homozygous for the long allele (LL) the depression term was significant ($\beta=.195$, $p=.005$), but not for the other two groups (SS: $\beta=.072$, $p=.423$, SL: $\beta=-.017$, $p=.781$). To further understand the interaction, the regression lines for girls by genotype were plotted (Figure 13). The figure illustrates a similar pattern for girls carrying at least one copy of the 's' allele (sl or ss) but more awakenings for girls homozygous for the 'l' allele who were exposed to antenatal depression.

⁴⁰ The analysis was repeated using sleep duration over the 24-hour period and the results did not change.

Table 34: Summary of Hierarchical Regression Analysis for infant sleep duration and awakenings at 24 months of age. Coefficients for Step 1,2 & 3 are after inclusion of 3-way interaction term in Step 4.

	Sleep Time		Awakenings	
Variables				
Step 1	β	p	β	p
Postnatal Depression	-.069	.020	.027	.360
Gender	-.034	.228	-.047	.088
Ed. Qualification	.037	.164	.026	.314
Alcohol	.024	.355	.023	.377
Smoking	.013	.597	.078	.002
Crowding	-.044	.092	.053	.037
Marital Status	-.033	.228	-.019	.487
Maternal Age	.014	.650	.027	.362
Step 2				
Antenatal Depression	.027	.332	-.039	.138
5-HTTLPR	.095	.001	.012	.666
Step 3				
Depression x Gender	.001	.980	-.040	.141
Depression x 5-HTTLPR	-.001	.972	-.019	.477
5-HTTLPR x Gender	.027	.337	.028	.300
Step 4				
Depression x 5-HTTLPR x Gender	.048	.078	-.055	.038
	R ² =.02 F(14,1611)=2.33, p=.003		R ² =.022	
			F(14,1622)=32.63, p=.001	
	N=1,626		N=1,797	

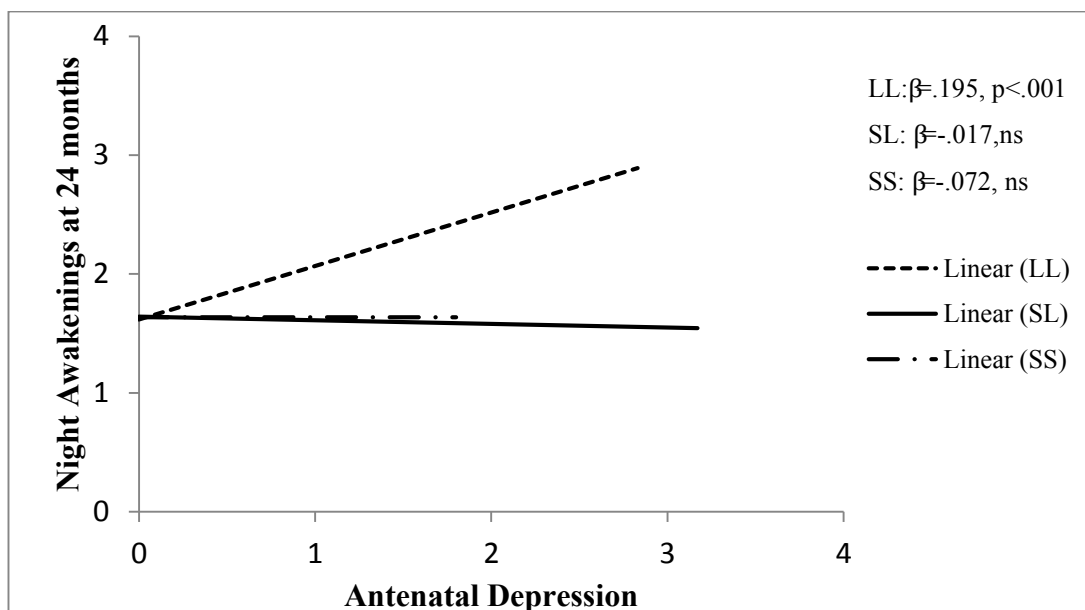


Figure 13: Linear Relations between antenatal depression and night awakenings at 24 months as a function of 5-HTTLPR for girls, Depressed category, top 15% of scorers.

Summary of Findings

There was evidence to suggest that 5-HTTLPR did moderate the association between antenatal depression and infant awakenings at 24 months of age. The association was found to be significant for girls and when stratified by genotype was found to be strongest for girls homozygous for the long allele.

3.4 DISCUSSION

The aim of this study was to examine the potential moderating role of 5-HTTLPR on the association between antenatal depression and infant sleep. The balance of the findings was that there was little evidence of a moderating effect. 5-HTTLPR was not found to moderate the association between antenatal depression and infant sleep for any of the sleep variables in ALSPAC, or for the majority of the sleep variables in the Generation R cohort.

There was some evidence at 24 months of age, in the Generation R cohort, that 5-HTTLPR did moderate the association between antenatal depressive symptoms and nighttime awakenings. Unexpectedly, the association between more severe depressive symptoms and more nighttime awakenings proved the strongest in girls homozygous for the long allele and weaker for carriers of at least one copy of the short allele. The regression lines for individuals homozygous for the short allele and heterozygous indicated no difference between these two groups.

To investigate whether the significant GxE interaction was consistent with a diathesis-stress model or a differential susceptibility model, the criteria outlined in the previous chapter were applied (Belsky, et al., 2007). The criteria stipulating that the moderator be independent of the outcome and predictor were met; indeed no association was found between 5-HTTLPR and sleep or antenatal depression. However, the criterion specifying that a clear cross-over be visible in the illustration of the slopes was not met. This suggests the evidence is more consistent with a diathesis-stress/dual-risk model rather than the differential susceptibility model. The stressor used here ranged from neutral to negative, from absence of depressive symptoms to severe symptoms. So it gives no indication as to whether the same girls might expect better outcomes following exposure to a positive or supportive environmental exposure. Hence the results are unable to support the differential susceptibility hypothesis.

Although a notable finding, the evidence that one polymorphism may contribute to infant awakenings requires further exploration and replication; as the finding was not replicated at 6 months of age in the Generation R cohort or at any time points within the ALSPAC cohort. Given the number of planned regression analyses ($n=12$) the significance level of this association would not withstand a standard Bonferroni correction ($\alpha/n=.05/12=.004$). Therefore, it has to be considered that this may be a

spurious finding. The absence of similar studies and the very limited and contradictory evidence suggesting carriers of the long allele as the vulnerable group, further underscore the need to interpret this finding cautiously until further replication.

In this analysis the long allele may be identified as the allele conferring “risk”. Given the large number of studies and meta-analyses which have discussed the contradicting role of 5-HTTLPR this finding should be interpreted cautiously. This finding in combination with the aforementioned literature would suggest that the role of 5-HTTLPR as a moderator of early life adversity and later child development may not be as straightforward as previously thought. The increasing amount of literature would suggest that due to methodological limitations of previous publications such as the ones discussed earlier (for example small sample size) our understanding of the role of 5-HTTLPR may be skewed. Until fully powered studies have replicated these findings the role of 5-HTTLPR needs to be interpreted cautiously.

3.4.1 The findings into context

The results of this chapter (with the one possible exception of awakenings at 24 months in Generation R), support the contention that 5-HTTLPR did not moderate the association between antenatal depression and infant sleep. Similar evidence for different infant outcomes has been reported by Braithwaite and colleagues (2013) using the ALSPAC cohort, where 5-HTTLPR was not found to moderate the association between antenatal anxiety and emotional and behavioural problems from 4 to 13 years of age.

The association between higher depressive symptoms and higher awakenings which was found to be strongest in girls homozygous for the long allele, can only be indirectly supported by evidence from Oberlander and colleagues, who reported in a smaller sample, that the association between antenatal exposure to SSRIs and externalizing behaviour was strongest in males homozygous for the long allele, and the finding of Barclay et al. (2011) who reported a main effect of 5-HTTLPR on poor sleep quality for males. In contrast most other studies either report the s allele to be the risk allele, or find no effect at all. In light of this evidence it can only be concluded that the role of the serotonin transporter gene 5-HTTLPR is more subtle and perhaps complicated than was assumed after the surge of studies identifying it as a vulnerability gene.

There are a number of methodological issues that may have contributed to null findings. These are considered here.

First, this study examined antenatal depression as a marker of adversity early on in life. The research on antenatal depression and child development has not conclusively identified whether the effects of antenatal depression may be different according to the severity of symptoms, the length of exposure and the timing of exposure. For example, exposure during different trimesters may have a different effect, as would exposure to more severe depression. For this study depression symptoms during the third trimester were used. Other stressors which have been identified and are reported to interact with 5-HTTLPR including maltreatment, abuse and neglect all occur in the postnatal period. It is possible, therefore, that the stressor here occurred too early, was not strong enough, or did not last long enough to see an interaction effect with 5-HTTLPR on infant sleep, an idea discussed by others also reporting null findings (Chipman et al., 2007).

Second, sleep is likely to be influenced by a number of factors including other genes (e.g. CLOCK, PER 1,2, and 3 and CRY 1 and 3) and environmental factors such as parenting and sleeping environment. Antenatal depression may interact with different genes or a combination of genes or environmental factors to predict sleep.

Finally, as Duncan and Keller have suggested the majority of studies published so far have been underpowered and disproportionately subject to Type I errors (Duncan & Keller, 2011). The high rate of positive yet underpowered results, combined with the known difficulty of publishing negative results, may contribute to a skewed view of the role of 5-HTTLPR.

It is worth noting here that Generation R used a bi-allelic classification (SS vs. LL), whereas ALSPAC used a tri-allelic classification (SS, SL_G, L_GL_G vs. L_AL_A). The tri-allelic classification provides additional information about the alleles allowing thus more accurate categorisation between high and low activity alleles. For this reason the analysis in ALSPAC was not conducted using the bi-allelic classification alone. Although it is possible that this may affect findings in the comparison between high and low activity alleles it is unlikely given the small frequency of L_G that this would have made a difference (for example in ALSPAC SS (16.6%), L_GL_G(.8%), L_AL_A(25.4%)).

3.4.2 Strengths and Limitations

This was a novel investigation examining the potential moderating role of 5-HTTLPR on the association between antenatal depression and infant sleep, extending and adding to the limited number of studies. This study examined 5-HTTLPR as a moderator early

in life and with a specific focus on adverse environmental exposure occurring before birth. The aims were addressed using two large population based cohorts. The large sample size of these cohorts is a particular strength of this investigation. As discussed in the introduction, Duncan and Keller have pointed out that studies so far have failed to achieve the necessary statistical power to show these effects and in many cases samples were as small as $n=75$. The study most closely resembling the present design, by Pluess and colleagues, reported an effect size $f=.004$. Taken together with the guidelines by Duncan and Keller, that would suggest that to detect that effect size with 80% power, a sample size of 2412 participants would be required. Given these calculations the ALSPAC cohort was sufficiently powered to find such an effect although the Generation R study was slightly underpowered. Indeed post hoc analyses indicated that the ALSPAC sample was of sufficient size to detect an effect size $f=.003$ with 80% power. The Generation R cohort, with a smaller sample size, and with 80% power, could have detected an effect size $f=.01$ to $f=.007$ (depending on the data available, at different time points $n=1269$ and $n=1782$ respectively).

Large prospective, population-based samples of normal, non-clinical populations, such as those examined here, avoid selection bias to a large extent, making the findings more generalizable. The study population were limited to participants of Caucasian ethnicity, ensuring this was a relatively homogeneous sample. This decision was based on evidence suggesting that allele distribution of 5-HTTLPR is different across ethnic groups and may function differently in these groups (Kunugi et al., 1996; Serretti, Kato, De Ronchi, & Kinoshita, 2006). Although this may somewhat restrict generalizability at the same time makes the findings more robust.

The genetic data used in the study were all found to be in Hardy–Weinberg equilibrium and, where possible, a triallelic classification was used (ALSPAC cohort).

Furthermore, the study employed established and widely-used measures for the assessment of depression.

Finally, in both cohorts longitudinal data was available.

The study also suffered some limitations. Data on maternal mental health and infant sleep were all collected by maternal reports. In large-scale studies, such as these, it is potentially time consuming and expensive to use more detailed and objective measures such as clinical diagnosis or objective assessment of sleep. Mothers are likely to be the

ideal informer, as they are observing a variety of different behaviours, sleeping habits and routines that may not be available in short observations to a researcher. However, their reports are also likely to suffer from bias, especially in the case of higher depressive symptoms. Although there may actually be an element of distortion in depressed mothers' interpretation of their children's behaviour a review by Richters (1992) suggests that this claim is actually over-represented in the literature without sufficient evidence to support this. Furthermore, sleep patterns may also depend on temporary circumstances such as sickness or teething (Owens & Witmans, 2004), of which a mother would be aware. With respect to sleep in particular, comparisons between maternal reports and actigraphy of infant sleep report an overestimation of time spent asleep in maternal reports (Nixon, et al., 2008) and an underestimation of sleep problems compared to self-report (Owens, et al., 2000). In Chapter 4 of this thesis a comparison of maternal reports and actigraphy data indicated an agreement in time going to bed but no significant associations for time asleep, wakefulness during the night or number of awakenings.

A second limitation of the study is the use of questionnaires for the assessment of infant sleep, which has not been extensively validated. Every effort was made to ensure that coding of sleep data was conducted in the same way across cohorts, with the same rules applying for dealing with outliers and Winsorising.

3.4.3 Conclusion

In conclusion, this study has shown that across two large prospective population based cohorts in the UK and The Netherlands, the effect of antenatal depression on infant sleep was overall not moderated by the serotonin transporter gene. Future investigations of this question should expand to include other genes, perhaps ones more closely associated to sleep function and include a more objective measurement for sleep.

Chapter 4: An investigation of the
association between antenatal
maternal depression and infant sleep,
using detailed observational
measures

4 Chapter Overview

This chapter describes a study investigating the association between maternal antenatal depression and infant sleep using detailed observational measures for both mothers and their infants. Whilst these measures are more independent and robust than questionnaire measures which are more commonly used, they are more time consuming and challenging to undertake for both participants and researchers. In part because of this, recruitment to this study proved more challenging than expected and, despite extensive efforts and review of recruitment strategies, insufficient numbers were recruited to adequately power the study. Nevertheless, several exploratory analyses of interest were undertaken which confirmed an already established association between antenatal depressive symptoms and shorter infant sleep duration. Important lessons were learnt for the conduct of future studies in this field.

This study uses data from 16 mothers and infants followed from the antenatal period to 5 months postpartum. During both antenatal and postnatal periods data on mothers depressive symptoms, anxiety and sleep was collected as well as actigraphy data and morning cortisol levels. For infants, actigraphy, morning cortisol levels and maternal reports on infant sleep and behaviour were collected.

4.1 INTRODUCTION

Antenatal depression has been associated with infant sleep; more specifically, the evidence to date suggests that antenatal depression is associated with shorter sleep duration and more night awakenings and sleep problems.

The review of this literature in Chapter 1 identified three key methodological issues in the published studies: First, the majority of studies relied either on maternal report of infant sleep or on short-term observations of infant sleep. Only one study was identified which used actigraphy to assess sleep (Armitage, et al., 2009).

Second, the studies utilized either self-report or a combination of diagnostic and self-report tools to assess maternal mental health, but only one study used clinical diagnosis alone to identify women with depression (Jones, et al., 1997).

Third, the age of infants at the time of assessment varied significantly from day 1 to 30 months of age. Due to the rapid developmental changes, including changes in sleep occurring during the first years of life, it is difficult to generalize the findings from one time point to another.

These issues need to be addressed adequately if a detailed understanding of mechanisms is to be possible. Although the question of whether antenatal depression is associated with infant sleep has received some attention, much is yet to be determined particularly with respect to the exact mechanisms through which the transmission of risk occurs. Four plausible and unexplored, biological and environmental mechanisms are considered here.

4.1.1 Mechanisms

4.1.1.1 *Maternal cognitions*

Maternal cognitions about infant sleep have been shown to be a determinant of infant sleep and more specifically of sleep problems (Sadeh, et al., 2010) and to mediate the well-established association between postnatal depression and disturbed infant sleep (Teti & Crosby, 2012). It has been shown that maternal cognitions relating to infant sleep problems such as setting limits, anger at the infant's demands, and doubts about parenting competence are significantly associated with infant sleep problems (Morrell, 1999). A study by Sadeh et al. (2007) examined maternal and paternal cognitions about

sleep in a sample of infants with and without sleep-disturbances. The authors reported that higher scores on cognitions relating to limit setting difficulties were reported for the group of infants with sleep-difficulties. Paternal cognitions were associated with more night awakenings independently of maternal cognitions suggesting, that when both parents experience these difficulties infants may be at increased risk for disturbed sleep. A recent study by Tikotzky and Sadeh (2009) assessed maternal cognitions about sleep during the third trimester of pregnancy. Infant sleep was assessed through actigraphy at 1, 6 and 12 months of age during which time points data on maternal cognitions was also collected. Early maternal cognitions about sleep relating to infant distress were associated with a higher number of reported and observed awakenings at 6 months. Cognitions about the importance of limiting parental involvement were associated with more consolidated sleep. This is the first study to demonstrate that parental cognitions before birth may be associated with infant sleep. Taken together the literature suggests that these cognitive processes may disrupt parent-child interactions and could potentially lead to impairments in the development of infant self-regulation.

4.1.1.2 Temperament

Antenatal depression has been associated with reports of negative or reactive temperament, fussiness and crying, higher levels of withdrawal, and less optimal performance on the Neonatal Behaviour Assessment scale (Davis, et al., 2007b; Field, 2011; Field, Diego, Dieter, et al., 2004; Field, et al., 2006; Lundy, et al., 1999a; McGrath, et al., 2008; Werner, et al., 2007).

A number of studies also suggest there is an association between temperament dimensions and infant sleep and more specifically, it seems that sleep problems are over-represented in infants with difficult temperament (discussed in Chapter 2) (Carey, 1974; Ednick, et al., 2009; Halpern, et al., 1994; Keener, et al., 1988; Schaefer, 1990b; Scher, et al., 1998; Spruyt, et al., 2008; Weissbluth, 1983).

4.1.1.3 Maternal and Infant Cortisol

The Hypothalamic Pituitary adrenal axis has been identified as a biological pathway through which antenatal depression may confer risk to fetal and infant development. Cortisol, a glucocorticoid hormone, is the end product of the HPA axis and a reliable tool for investigating the functioning of the HPA axis.

Maternal Cortisol and Antenatal Depression

During pregnancy, secretion of cortisol is also regulated by the placental and fetal membranes; the placenta secretes Corticotropin Releasing Hormone (CRH) into the fetal and maternal bloodstreams (Field & Diego, 2008). From the eighth week of gestation secretion of cortisol increases exponentially and peaks during the third trimester.

Antenatal depression has been associated with higher levels of maternal cortisol (Field, Diego, Dieter, et al., 2004; Pluess, Bolten, Pirke, & Hellhammer, 2010; Rothenberger, Moehler, Reck, & Resch, 2010). It has been hypothesized that elevated maternal levels may lead to higher fetal cortisol levels. Evidence suggests that maternal cortisol crosses the placenta and may account for up to 40% of variance in fetal levels (Gitau, Fisk, & Glover, 2001). In the context of maternal depression this may of particular importance as women with antenatal depression may have higher levels of maternal cortisol compared to those without depression (Lundy, et al., 1999b; Sandman et al., 2006). Following cognitive behavioural treatment for women with sub-clinical levels of depression and stress, Richet et al. (2012) reported a decrease in the morning cortisol levels of women who had received the therapy compared to those who had not.

Maternal Cortisol and Offspring Development

Elevated maternal cortisol levels have been associated with preterm delivery, lower fetal weight, negative infant temperament and lower Apgar scores (Bolten et al., 2011; de Weerth, van Hees, & Buitelaar, 2003; Goedhart et al., 2010; Ponirakis, Susman, & Stifter, 1998). Amniotic fluid cortisol, collected during the second trimester, has been associated with infant cortisol response to separation-reunion stress at 17 months of age in a sample of 125 mothers and infants independently of antenatal obstetric and socio-economic factors and parent-child attachment (O'Connor, Bergman, Sarkar, & Glover, 2012).

Antenatal Depression and Offspring Cortisol

Antenatal depression has also been associated with infants response to novelty, baseline cortisol levels in response to a stress task in 2 year olds, elevated cortisol responses during the first day of school and elevated diurnal cortisol at 10 years of age and higher resting cortisol throughout the day in adolescents (Bergman, et al., 2007; Davis et al., 2007a; de Bruijn, van Bakel, Wijnen, Pop, & van Baar, 2009; Dougherty et al., 2013; Gutteling, Weerth, & Buitelaar, 2005; O'Connor, et al., 2005). Furthermore, antenatal

maternal anxiety during the second trimester was associated with a flattened cortisol daytime profile in adolescents 14-15 years of age (Van den Bergh, 2007). In this sample the cortisol daytime profile in girls, was associated with depressive symptoms whilst controlling for maternal smoking, birth weight and postnatal anxiety. A large study (n=1,630) reported that cortisol awakening levels of individuals (aged 18-65) with parental history of depression or anxiety was similar to that of individuals with current depression or panic disorder with agoraphobia. Both groups had significantly higher levels compared to individuals without parental or current depression (Vreeburg et al., 2010). This evidence taken together suggests that antenatal depression may have long lasting influences on the development and regulation of the HPA axis in the offspring.

Although this has been hypothesized as key to the programming effects of antenatal depression on infant development the exact mechanism is not yet fully understood. The studies provide with promising results however, they also vary significantly in methodological issues, including the type of antenatal stress (e.g. depression, anxiety, life events), the method of measuring cortisol (e.g. saliva or plasma cortisol) and the age of participants which ranged from infancy to adolescence.

4.1.1.4 Maternal sleep

A final variable of interest in this study is maternal sleep for the following reasons:

First, sleep disturbances are common during pregnancy. They occur as a result of hormonal, physiological and physical changes to the mother for example, rise in steroid hormones, estrogen and progesterone levels and added discomfort due to the developing fetus. This may continue into the postnatal period due to the precipitous drop in hormones after delivery and of course due to the irregular feeding and sleeping schedule of the infant (Sahota, 2003).

Second, disturbances in sleep are a key symptom of a number of psychiatric disorders and have been implicated in both the initiation and maintenance of depressive symptoms (Armitage, 2007). There is also evidence to suggest that sleep quality early in pregnancy is negatively associated with depressive symptoms in the third trimester (Kamysheva, Skouteris, Wertheim, Paxton, & Milgrom, 2008; Skouteris, Germano, Wertheim, Paxton, & Milgrom, 2008).

Third maternal disturbances during pregnancy have been shown to have negative consequences for the mother, the labour and delivery process and the child. Poorer sleep

quality during pregnancy has been associated with preeclampsia, shorter sleep duration and in late pregnancy with increased caesarean section rates. Sleep deprivation antenatally has also been associated with postpartum depression (Chang, Pien, Duntley, & Macones, 2010; Wolfson, Crowley, Anwer, & Bassett, 2003). Furthermore, women averaging less than 6 hours of sleep had longer labour (29h vs. 20h labour) and a higher rate of caesarean births (<6hours: 37%, 6-6.9 hours: 34%, more than 7 hours: 11%) (Lee & Gay, 2004). Less total sleep time on the night before hospitalization was associated with elevated perception of pain and discomfort during labour (Beebe & Lee, 2007). In a sample of 92 women during their residency training, 50% of residents averaged 1 night per week without sleep during 1st & 2nd trimester and 44% 1 night per week without sleep during 3rd trimester. In this sample an increased risk of preterm labour was found (Osborn, Harris, Reading, & Prather, 1990). 4,412 women residents had higher rates of preterm labour compared to partners of male residents (11 vs. 6%) and preeclampsia (8.8 vs. 3.5%). Women working more than 100h per week during 1st trimester had higher risk of preterm delivery (Klebanoff, Shiono, & Rhoads, 1990). In a sample of 942 women, sleeping less than or equal to 8h during the 2nd and 3rd trimesters was identified as a risk factor for small for gestational age less than 5th centile (Abeysena, Jayawardana, & De A Seneviratne, 2009). A recent meta-analysis of studies examining the risk of preterm delivery following shift work, an extreme form of sleep deprivation and disturbance to circadian rhythmicity, reported a slightly increased risk of preterm delivery (1.03, 95%CI 0.93-1.14), low birth weight (1.27, 95%CI 0.93-1.74) and small for gestational age (1.12, 95%CI 1.03-1.22) (Bonzini et al., 2011).

A mechanism through which disrupted sleep may affect pregnancy outcomes and foetal development has been proposed by Okun et al (2009) which suggests that disturbed maternal sleep during pregnancy is associated with increased inflammatory responses. These inflammatory responses may act as a biological pathway for adverse pregnancy outcomes. Particularly during the first 20 weeks of gestation key physiological changes occur, such as the remodelling of the maternal vessels perfusing the placenta to increase placental blood flow. Evidence suggests that increased inflammation may inhibit this trophoblastic invasion which is necessary for remodelling. Thus, particularly during the first 20 weeks of gestation, disturbed maternal sleep may act as an independent biological pathway to altered foetal development.

For these reasons, it was hypothesized that maternal sleep disturbances may be a key unexplored variable in explaining how antenatal depression impacts on infant sleep.

This chapter will focus on the following aspects of infant sleep; sleep duration and night awakenings (both in terms of frequency of awakenings and duration of wakefulness over the night period). This chapter focuses on these variables for two reasons: first, the evidence that antenatal depression is associated with infant sleep has revealed three aspects of sleep to be most affected (sleep duration, night awakenings and sleep problems) and second, to keep consistency across the sleep variables examined in the other chapters of this thesis. Unlike Chapters 2 and 3, this chapter does not assess sleep problems as the first few months of life were determined to be too early to assess sleep problems.

4.1.2 Aims

The primary aims of this study were

- i) to examine the association between maternal depressive symptoms and infant sleep as assessed through actigraphy and maternal reports
- ii) to examine the agreement rates between actigraphy and maternal report of infant sleep in this sample.

It was hypothesised that

- i) Maternal depressive symptoms would be associated with more disturbed infant sleep, more specifically, shorter sleep duration, more night awakenings and longer duration of wakefulness during the night
- ii) It was hypothesised that actigraphy (in particular, night awakenings and sleep onset) would be associated with maternal reports of infant sleep.

Secondary Aims

It was hypothesised that maternal depressive symptoms would be associated with:

- i. higher scores on maternal cognitions about infant sleep, particularly with difficulties in setting limits
- ii. higher temperament scores on the scale measuring distress
- iii. higher levels of maternal and infant morning cortisol
- iv. disturbed maternal sleep, particularly, shorter sleep duration and more awakenings

4.2 METHODS

4.2.1 Design

This was a longitudinal community-based observational pilot study. The study received ethics approval from the Berkshire Research Ethics Committee as well as the necessary Research & Development approvals for research (10/H0505/76).

4.2.2 Procedure

4.2.2.1 Recruitment

Mothers were recruited during their third trimester of pregnancy from the Oxford area and were contacted once during pregnancy and once postnatally. I approached mothers after a routine visit with community midwives. The midwife would establish that the mother was happy to be informed of the study and I would briefly describe the study to the potential participants. Every participant received an information pack. I collected contact information from the participants in order to contact them after they had sufficient time to review the information and decide whether they would like to participate in the study. Recruitment started in March 2011 and concluded in June 2012.

Inclusion Criteria

- i. Pregnant women in their third trimester of pregnancy between the ages of 18-50 who are fluent in English;
- ii. Participants who were willing and able to give informed consent for participation in the study;
- iii. Living in the wider Oxford area.

Exclusion Criteria

- i. Mother was not be cohabiting with the child;
- ii. Mother suffered from severe psychiatric diagnosis (other than depression/anxiety);
- iii. Mother suffered from life-threatening or other serious illness;
- iv. Mother unable to converse in English;
- v. Blind people were also excluded due to the significant disruptions in sleep, which could confound the results;

- vi. Fathers who were not cohabiting with their child. In this case only fathers would be excluded if the mother wished to participate. Fathers' participation would not impact on the mothers or her child's participation;
- vii. Infant born at < 35 weeks gestation and with birth weight of < 2000 grams;
- viii. Parents of infants with a life threatening illness would be excluded as would parents with infants with congenital abnormalities as these factors would significantly confound the study.

4.2.2.2 Antenatal Home Visit

Mothers were contacted through telephone, email or post, according to their preferred method of contact and a home visit was scheduled. During the home visit the mother completed a battery of questionnaires on socio-demographic characteristics, the EPDS, the Pittsburgh Sleep Quality Index (PSQI) and the Stressful life events questionnaire (all measures are described in details in the Measures section). I then proceeded to the clinical interview. Details on the administration of the clinical interview are provided in Section 4.2.4.1.1. Participants were then presented with the actiwatch and instructions on wearing the actiwatch and completing the diary. They were also given 4 tubes for collection of morning saliva samples with instructions. Mothers were asked to inform me when they had collected the samples to schedule collection of the samples. After two weeks I contacted the participants to collect the actiwatch, during which period participants were given a voucher (of £20) for their participation. If participants were happy for their partners to participate, a detailed information sheet and questionnaire were given to them to be passed on. Fathers were asked to complete questionnaires at the same time point as mothers.

4.2.2.3 Postnatal Home Visit

Mothers were contacted 5 months postnatally. During this visit they completed a set of questionnaires (on depression and anxiety, maternal sleep, demographics & infant feeding) and the interview for diagnosis of depression was administered again to record any changes. Mothers were given the actiwatch as in the antenatal phase with instructions and two diaries to complete (to complete both the activities of the mother and child). Mothers were given a mini actiwatch for their baby. The actigraph was placed on the infant's ankle. Data was collected for 2 weeks. Mothers were asked again

to collect saliva samples in the same way they did during the antenatal home visit (4 samples of saliva every 15 minutes for the first hour of the day, for 1 day) as well as saliva samples of their child in the exact same way (in total 8 samples for mother & infant). Samples were kept in the freezer. If during the antenatal phase mothers had indicated co-habiting with a partner, they were asked to forward a postnatal questionnaire to them.

4.2.3 Participants

19 women were recruited in the study, however 2 were excluded from this analysis. One mother had already given birth (prematurely) at the time of the antenatal visit and had not informed the researcher. At this point antenatal questionnaire data and the SCID were collected (baby was 2 days old). For the postnatal visit, I was unable to contact the mother. The telephone number given was no longer in use and on two occasions I visited the participant's home but there was no response. The other participant completed the questionnaire and SCID data but withdrew her participation due to time commitment of the study and for this participant there was no actigraphy data. Data from both these participants were not included in the analysis. The table below provides demographic characteristics of the sample $n=17$. There were $n=16$ infants for whom questionnaire data was available and $n=14$ infants for whom actigraphy data was available. All babies were born healthy and full term. At the time of assessment the majority of babies ($n=12$) were breastfed or received a combination of breastfeeding and bottle-feeding. Demographic information on the sample is presented in Table 35.

Table 35: Demographic characteristics of Study

	<i>n</i> =17	Mean (SD), Range/%
Participant Characteristics		
Age		30.2 yrs (2.14), 27-34
No. of weeks pregnant at baseline assessment		33 wks (5.6), 25-39
Ethnicity (White)	16	94.1%
Married/ living together		100%
Socio-economic indicators		
Working (full or part time)	12	70.6%
Educational Qualification (undergraduate and above)	13	76.5%
Financial Income (of household)	5	29.4%, <£25,000
	5	29.4%, <£40,000
	7	41.2%, ≥£40,000
Depression History		
History of depression in the past	4	23.5%
History of sub-clinical anxiety in the past	4	23.5%
Antenatal depression – DSM diagnosis	0	0%
Postnatal depression – DSM diagnosis	4	23.5%
Clinical variables		
Antenatal depressive symptoms (EPDS)	17	4.37 (3.01), 2-11
Postnatal depressive symptoms (EPDS)	17	4.87 (3.68), 1-11
Anxiety (STAI)	17	29.12 (5.22), 23-37
Number of Life Events: median	17	0 (0.89), 0-2
Smoking during pregnancy	0	0%
Alcohol during pregnancy	7	41.2%(between 1-5 units weekly)
Infant characteristics		
	<i>n</i> =16	
Infant gender:		7 male (44%), 9 female (56%)
Infant age (months)		5.8 months(0.8), 4.2-6.8
Birth order (first born)	7	44%
Prematurity	0	0%
Birth weight (kg)	16	3.67(0.24), 3.33-4.03
Days spent in Special Care Baby Unit	0	0%
Feeding : Breast	6	37.5%
Bottle	4	25%
Both	6	37.5%

4.2.4 Measures:

4.2.4.1 *Mental Health*

4.2.4.1.1 Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) is a semi structured psychiatric interview for major DSM-IV Axis I diagnoses (First, Spitzer, Gibbon, & Williams, 2002). Administration of the SCID may take from 15 minutes up to a few hours depending on the psychiatric co-morbidity of a participant. The interview focuses on diagnosis rather than symptomatology. It is designed hierarchically with decision trees that guide the researcher when to terminate administration of each module. Symptoms are rated as absent (1), subthreshold (2) or threshold (3, i.e.: criterion is met). To meet criteria for diagnosis of depression the participant must meet threshold criteria in 5 out of 9 symptoms as well other diagnostic factors such as impairment in social or family functioning. Participants were asked two standardized screener questions for depression and General Anxiety Disorder only. If they responded positively I continued with the rest of the module. Participants were also asked about their history of depression and generalized anxiety disorder (Appendix 39). Information was also collected on medication given to the participant for depression and generalized anxiety disorder.

4.2.4.1.2 Maternal depressive Symptoms

Maternal mood was assessed ante- and postnatally using the EPDS. This measure has already been described in detail in Section 2.2.1.3.1, page 79 and is included in Appendix 30.

4.2.4.1.3 Paternal depressive Symptoms

Depressive symptoms in fathers were assessed also using the EPDS. This measure has been validated for use with fathers (Edmondson, Psychogiou, Vlachos, Netsi, & Ramchandani, 2010; Matthey, Barnett, Kavanagh, & Howie, 2001). A cut-off of 10 was found to be the optimal score for screening for depression (sensitivity of 89.5% and specificity of 78.2%).

4.2.4.1.4 Maternal Anxiety

Anxiety was measured during pregnancy using the Trait scale of the State Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, & Edward, 1970), a widely used and validated measure in the perinatal period, (see Appendix 33). The STAI consists of 20 items ranging from 1 (Not at all) to 4 (Very much so). The total score of the STAI is calculated by adding the items and ranges from 20-80.

4.2.4.1.5 Maternal Stressful Life Events

The Stressful Life Events Questionnaire (SLEQ) was used to assess maternal exposure to traumatic experiences during pregnancy (Goodman, Corcoran, Turner, Yuan, & Green, 1998). This is a 26 item questionnaire adapted from the Inventory of Ranked Life Events for Primiparae and Multiparae women (Barnett, Hanna, & Parker, 1983) which has been previously used in antenatal mental health research and has been shown to be related to infant cognitive ability and observed fearfulness (Bergman, et al., 2007). In this study participants were asked to indicate whether they had experienced any of the items since the beginning of their pregnancy and how much it had affected them (little or a lot, see Appendix 34).

4.2.4.2 Parental and infant Sleep

4.2.4.2.1 Actigraphy

Rest activity patterns were measured using light and motion sensor actigraphy. Mothers and babies were instructed to wear the actiwatches for 14 days (2 weeks mean recording = 12.3 days (r:6-15)). Mothers were given light and motion sensor actiwatches (Actiwatch L) and babies were given motion sensor actiwatches (Actiwatch Mini) (Cambridge Neurotechnology Ltd, UK). Mothers were asked to wear the actigraph once during pregnancy (for 2 weeks) and once postnatally (at the same time as their babies). Mothers wore actigraphs on their non-dominant wrist and babies on their ankle. For the Mini actiwatches babies were given a normal strap (similar to the mother's) and an additional custom made strap constructed of elasticated tubular support bandage as an alternative to minimize skin irritation. Mothers wore the same Actiwatch pre and postnatally to reduce variability among the devices. Participants also completed daily diaries (for example see Appendix 37) for themselves and their babies which included information on when the watch was removed and put back on (watches were removed prior to activities during which they could get wet for example shower/swimming), and

when they went to bed/got up. Participants were encouraged to complete as much information as possible about their daily activities such as lying awake in bed, times of meals, and calm activities such as watching TV or reading. They were also asked to complete feeding times for babies, particularly during the night.

Preliminary Analysis of Actigraphy Data

The actiwatches were set to record at 1-minute epochs. After each battery replacement the actiwatches were calibrated. Data were downloaded onto a computer via a USB reader and were analysed using Actiwatch software version 7.23, Cambridge Neurotechnology, UK. Actograms including rest-activity and light patterns were examined concurrently with the diaries and the activities on the diaries were transferred onto copies of the actograms to establish bed-times and get-up times and any periods during which the Actiwatch had been taken off. Gaps in the actograms during the day were substituted with mean daily activity if they lasted between 10 minutes and 3 hours and if the participant had recorded what they had been doing during the time (for example shower or swimming). In cases of longer gaps that whole 24-hour day was excluded from the analysis.

A number of variables were derived and are explained below. All definitions presented here are in accordance with the actigraphy software manual. All variables were derived by averaging the scores over the number of nights for which full actigraphy data was available.

1. **Time in bed:** refers to the time elapsed between Bed Time and Get-up times as set by me in accordance with the participant's diary.
2. **Assumed sleep = Sleep period (SP):** The total elapsed time between sleep start and sleep end times.
3. **Actual sleep time during the night = Nighttime total sleep time (nTST):** The total time spent in sleep according to the epoch-by-epoch wake/sleep determined by the algorithm and is equivalent to assumed sleep minus wake time (threshold for wake was a score of 40 and above).
4. **Actual sleep (%) = Sleep efficiency:** Actual sleep time expressed as a percentage of the assumed sleep time.
5. **Actual sleep time during the day** (this was only used for infants as only one mother had day naps) = day-time total sleep time (dTST).

6. **Actual sleep time during the 24-hour period** (sum of nighttime sleep and nap time in the day following the night).
7. **Actual wake time during the night**: The total time spent in wake between sleep onset and offset as determined by the algorithm.
8. **Actual wake (%)**: Actual wake time expressed as a percentage of the assumed sleep time.
9. **Sleep latency**: The time between Bed Time and sleep start.
10. **Wake bouts**: The number of episodes of wakefulness during the nighttime.
11. **Number of Minutes Immobile**: The total number of minutes during the assumed sleep period where the counts per minute are below a predetermined “immobility” threshold. See below.
12. **Immobile time (%)**: Percentage of Number of Minutes Immobile/Assumed Sleep period.
13. **Fragmentation Index**: This is an indicator of restlessness. The sum of the “Mobile time (%)” and the “Immobile bouts ≤ 1 min (%)”. This is an indication of the degree of fragmentation of the sleep period, and can be used as an indication of sleep quality (or the lack of it).

Using the same software Non-Parametric Circadian Rhythm Analysis (NPCRA) was also conducted (Somerén et al., 1999). The software calculates an average activity curve. For all available days the software calculates the activity for every hour of the 24-hour period and determines the most active 10 hours (M10) and the least active 5 hours (L5). These can be used to examine the peaks and troughs of the circadian rhythm. The following variables were further calculated:

The Relative Amplitude (RA): is calculated by dividing the difference between M10 and L5 by the sum of M10 and L5 ($RA = (M10 - L5) / (M10 + L5)$). Scores range from 0 to 1 and higher scores reflect increased daytime activity and reduced activity during sleep.

The Inter-daily stability (IS): is a measure of consistency between the days; describing the strength of coupling of the rhythm to supposedly stable environmental zeitgebers

The Intra-daily variability (IV): gives an indication of the fragmentation of the rhythm. More specifically, it describes the frequency and extent of transition between periods of rest and activity.

4.2.4.2.2 Daily activities diary

Mothers were given a sleep/wake diary where they entered their daily schedule (see example, Appendix 37). This was used to account for times where the actigraph was removed (e.g. shower) and for feeding rhythm (disturbance of mother's sleep due to the infant).

4.2.4.2.3 Pittsburgh Sleep Quality Index - PSQI

The PSQI has been widely used to assess sleep quality in adults. It has also been shown to have good internal consistency and convergent and divergent reliability properties when used in a sample of pregnant women (Jomeen & Martin, 2007). It consists of 19 questions (see Appendix 32) and assesses a variety of factors relating to sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction (Buysse & Reynolds, 1989). These 19 items are grouped into seven component scores, each weighted equally on a 0-3 scale. The seven component scores are then summed to yield a global PSQI score, which has a range of 0-21; higher scores indicate worse sleep quality. The seven components of the PSQI are standardized versions of areas routinely assessed in clinical interviews of patients with sleep/ wake complaints. These components are subjective. The questionnaire was administered both pre- and postnatally to mothers and fathers.

4.2.4.2.4 Brief Infant Sleep Questionnaire (BISQ)

The BISQ was used to assess infant sleep via maternal and paternal report, where available. The questionnaire has been shown to distinguish well between control and clinical samples and to show agreement with actigraphy-derived sleep parameters and sleep diaries (Sadeh, 2004b). Questions on the BISQ address: 1) nocturnal sleep duration (between the hours of 7 PM and 7 AM); 2) daytime sleep duration (between the hours of 7 AM and 7 PM); 3) number of night wakings; 4) duration of wakefulness during the night hours (10 PM to 6 AM); 5) nocturnal sleep-onset time (the clock time at which the child falls asleep for the night); 6) settling time (latency to falling asleep for the night); 7) method of falling asleep; 8) location of sleep and 9) preferred body position. An additional variable for sleep during the 24-hour period was calculated, by adding the nocturnal sleep duration and daytime sleep duration and subtracting the duration of wakefulness during night hours.

4.2.4.2.5 Maternal Cognitions about Infant Sleep Questionnaire (MCISQ)

The questionnaire assesses maternal cognitions about sleep and consists of 20 items on a 6-point Likert-type scale ranging from strongly agree to strongly disagree. The questionnaire consists of 5 scales examining distinct maternal cognitions and of a total score (Morrell, 1999). The questionnaire assesses: Limit Setting which refers to parental difficulties in resisting the infant's demands and low threshold for responding to these demands, Anger referring to potential feelings of anger, regret and helplessness in the face of demands the infant presents with, Doubt indicating experiences of doubt and uncertainty as to whether their parenting is adequate, Feeding, referring to beliefs about the importance of feeding to soothe the infant and have worries about the child going hungry during the night, and finally Safety, referring to excessive concerns regarding cot death. A total score is calculated by adding all the above scales. Higher scores on the scales indicate greater concern, although they are not all directly comparable in terms of means and standard deviations as the number of items loading onto each factor is different (Limit Setting – 5 items, Anger – 5 items, Doubt – 5 items, Feeding – 3 items, Safety – 2 items).

4.2.4.3 Infant temperament

Infant behaviour was assessed using the Infant Behaviour Questionnaire (IBQ) during the postnatal visit by both parents (Rothbart, 1981). The questionnaire consists of 94 items relating to the infants' behaviour. Caretakers were asked to respond on the basis of the infants' specific behaviour during the past week. Responses range from 1=never, 2=very rarely, 3=less than half the time, 4=about half the time, 5=more than half the time, 6=almost always, 7=always and X=does not apply. The last option is included, as some behaviours may not have occurred during the past week. The questionnaire consists of 6 scales: activity level, smiling and laughter, fear, distress to limitations, soothability and duration of orienting⁴¹. The scales are defined here as in the original

⁴¹ The scales are defined here as in the original paper (Rothbart, 1981) Activity level refers to the child's gross motor activity, including movement of arms and legs, squirming and locomotor activity. Smiling and laughter relate to any situation in which the child performs these actions. Fear is defined as the child's distress and/or extended latency to approach an intense or novel stimulus. Child's fussing, crying or showing distress is measured in any of the following situations: waiting for food, refusing a food, being in a confining place or position, being dressed or undressed, being prevented access to an object towards which the child is directing his or her movement. Soothability refers to situations where soothing techniques are used by the caretaker or child and lead to reduction of fussing, crying or distress. Finally, duration of orienting refers

paper by Rothbart. Maternal report was used for temperament as only a small number of fathers (n=5) returned the questionnaires leaving a large number of missing data.

4.2.4.4 Cortisol

Cortisol was measured ante- and postnatally. Four samples within the first hour awake (first at waking and three more at 15 minute intervals thereafter) were collected by the mother for herself and her baby. Mothers were instructed to collect cortisol on any day during which the actiwatch was recording (with exception of the first day⁴²). Information was given to participants both verbally and written on how to collect and store the saliva samples for them and their babies (Appendix 38). Saliva samples for mothers were collected using one salivette per sample and for babies using two sorbette eye sponges. Participants were also asked to complete the date of collection, the time they went to bed and got up, and the exact times each sample was collected.

Salivary cortisol was measured by direct double-antibody radioimmunoassay utilising ¹²⁵I labelled cortisol. The inter- and intra-assay coefficients of variation (CV) were 4.1% and 5.9% respectively and the limit of detection when 100µl of saliva was used was 0.1µg/cml.

4.2.4.5 Socio—demographic information

The following information was also collected regarding socio-demographic characteristics of the participants.

Recruitment Phase:

- is this your first pregnancy,
- is this a multiple pregnancy
- how many weeks pregnant are you

Antenatal Phase:

- Participants first language and language to be used with baby
- Ethnic background
- Current marital situation

to child's vocalization and interaction with a single object over a sustained period of time with no sudden change in stimulation.

⁴² Actiwatches were set to start recording at midnight on the day of the home visit. Participants were asked not to collect saliva samples on the first morning as it was desirable to have data on the whole night prior to saliva collection.

- Educational qualification and household income level
- Information on any health problems (including mental health) and medication
- Was this a planned pregnancy
- Smoking and alcohol habits during pregnancy
- Partner's Age and educational qualification

Postnatal Phase:

About the Baby:

- Date of birth,
- Routine medical data (birth weight and gestation, any problems with delivery, any days spent in Special Care baby unit, any visits to the GP)
- Feeding mode (e.g. bottle or breastfed)

4.2.5 Statistical Analysis Plan

1. Feasibility of the Study

The first section of the Results covers issues relating to the feasibility and recruitment of this pilot study.

2. Analysis relating to Primary Outcome – Infant sleep

As this was a small exploratory study attention was also paid to associations with a p value over 0.05 and Bonferroni correction was not applied. Due to the small sample size, results may not be significant and so the consistency of findings is emphasized.

- 2.1. Descriptives and normality tests for all measures were first examined. The Shapiro-Wilk test for normality was utilized due to the small sample size.
- 2.2. Associations between ante- and postnatal maternal depressive symptoms and sleep variables were examined using Pearson and Spearman two-tailed correlations for infant sleep variables derived from actigraphy and maternal reports.
- 2.3. Agreement rates for infant sleep between actigraphy and questionnaires were examined using Pearson and Spearman two-tailed correlations.

3. Analysis relating to secondary outcomes:

- 3.1. Associations between maternal cognitions about infant sleep and depressive symptoms were examined using Pearson and Spearman two-tailed correlations.
- 3.2. Descriptives for infant temperament are presented in section 4.3.3.2. In this section associations between infant temperament and maternal depressive symptoms were examined using Spearman correlations.
- 3.3. Descriptives for maternal and infant cortisol are presented in section 4.3.3.3. This section examines the associations between maternal and infant cortisol and maternal depressive symptoms using Spearman correlations.
- 3.4. Section 4.3.3.4 examines differences between maternal antenatal and postnatal sleep using paired sample t -tests and Wilcoxon Signed Ranked tests. Associations between maternal depressive symptoms and maternal sleep were examined using Spearman correlations.

4.3 RESULTS

4.3.1 Feasibility of the Study

This study was designed as a fully powered and exploratory study which aimed to recruit $n=56$ according to power calculations based on previous literature. Recruitment targets however were not reached. Some of the reasons which may explain the difficulties faced with recruitment include: first, there is a large number of studies taking place in Oxford specifically targeting women during pregnancy which may have overwhelmed participants, during an already busy period in their lives. Second, this particular study required a substantial time investment on behalf of participants, which may have acted as a deterrent. Third, the study relied on the midwives' assistance to recruit, and this was in addition to an already very heavy workload.

The strategies adopted here have been used successfully to recruit similar population groups in other studies. Nevertheless, the specific difficulties faced here have given insight into best ways to identify and recruit this population, which are already utilized by newer studies in our group. These primarily include the use of social media and advertisements in NCT classes.

4.3.1.1 Recruitment

Recruitment Strategy 1: I and one of my supervisors (PR) met with the Community Midwives Supervisor prior to receiving ethical approval to identify possible recruitment strategies. During the meeting it was identified that community midwives would be able to help with this study by forwarding information packs to mothers during routine visits. Prior to start of recruitment, we met with midwives during their weekly meeting, presented the study and asked for their help with recruitment. I subsequently delivered 70 recruitment packs for dissemination, which included a screener questionnaire and a freepost envelope, however, none were received back. Through conversations with the midwives 3 reasons of why none were received back became apparent. Mothers were already overwhelmed with information from other studies taking place during pregnancy, were not interested in taking part in research and did not take a recruitment pack or the midwives did not always have time to give the recruitment pack/ did not want to overwhelm women with information on research studies.

Recruitment Strategy 2: I attended weekly education classes held at Children's Centres in Oxford and Kidlington. These classes are provided free of charge to parents-to-be and last about 4 hours. Classes consisted on average of 7-8 couples. I presented the study to the participating parents and asked for their contact details. All parents received an information pack. I attended 10 classes over a period of 12 weeks. 6 couples expressed an interest in the study of which 4 subsequently did not want to participate.

Recruitment Strategy 3: Through educational classes attended and conversations with the midwives it was suggested that I recruit participants through GP surgeries after the mothers' routine appointment. Two large surgeries were identified in the city of Oxford. I attended clinic days in these two surgeries. On average 3-4 women a day would be eligible to participate in the study. Only women in their third trimester were approached (excluding women in the very end of their pregnancy, ≥ 40 weeks). This proved the most successful recruitment strategy for this study.

4.3.1.2 Antenatal Phase

Mothers-to-be were very receptive to the study during the home visit and completed the questionnaires and SCID, which took between 20-45 minutes approximately. They were also very diligent with their reporting of daily activities and on few occasions (on average once per 2 week recording (range 0-3) had the watch off for more than 3 hours. Collection of saliva samples proved more challenging as participants did not always collect adequate saliva for analysis and on two instances did not inform the researcher to collect the saliva in time.

4.3.1.3 Postnatal Phase

The postnatal phase proved challenging in similar ways to the antenatal phase. Saliva samples particularly for infants were of smaller volume and in some instances although mothers were asked to collect saliva using two sorbettes at each sampling time simultaneously they only used one (see Appendix 38). Mothers were again very diligent in their reporting of theirs and their babies' daily activities. The infant actiwatch was strapped to the infant's ankle using tubigrip material to avoid causing irritation on the skin. This was a less robust material to the original strap provided and in some cases lost its elasticity early. This resulted in gaps in recording when the actiwatch came off but was not always noticed by the mother for a few hours, for example when in the house or the pram.

4.3.1.4 Partners' Participation

Partner participation was low $n=5$. For this reason it was not possible to incorporate partner recorded data in the analysis.

4.3.2 Analysis of Primary outcomes

4.3.2.1 Descriptives

Descriptives are presented for infant sleep assessed through actigraphy (Table 36) and through mother-rated questionnaires (Table 37). The data were found to be normally distributed with the exception of sleep during the night and the 24-hour period as reported by the mother⁴³. Where these variables appear non-parametric tests have been utilized.

Table 36: Descriptives of infant sleep at 5 months by actigraphy.

Infant Sleep - Actigraphy	n=14	
	Mean (SD)	Range
Bed Time Start (clock time)	19:50(00:22)	19:36-21:06
Time in Bed (hh:min)	12:46(00:19)	12:26-13:21
Assumed sleep during the night (hh:min)	11:48(00:40)	10:30-12:43
Actual Sleep time during the night (hh:min)	09:19(00:22)	08:54-09:52
Actual sleep % during the night (%)	83.19(3.72)	77.99-87.15
Actual sleep time over the day (hh:min)	01:17(00:18)	00:48-01:34
Actual sleep time over the 24-hour period (hh:min)	10:22 (0:46)	09:14-11:10
Awake time during the night (hh:min)	01:53 (00:27)	01:27-02:33
Sleep latency (min)	8 (1)	7-12
Immobile minutes (min)	510.30 (27.96)	478-547
Immobile minutes % over night (%)	75.79 (2.91)	73.65-80.13
Wake bouts (nighttime awakenings)	33.35 (2.036)	30-35
Mean duration of Wake Bouts (min)	2(0)	2-4
Fragmentation Index	49.71(4.7)	43.87-55.34
IS	0.52(.06)	0.46-0.60
IV	1.16(.04)	1.07-1.20
Relative Amplitude	0.84(.06)	0.78-0.91

⁴³ Actigraphy: Time in Bed: S-W=.88, df=14, p=.316, Assumed sleep during the night: S-W=.98, df=14, p=.951, Actual Sleep time during the night: S-W=.91, df=14, p=.48, Actual sleep % during the night : S-W=.94, df=14, p=.678, Actual sleep time over the day: S-W=.84, df=14, p=.153, Actual sleep time over the 24-hour period: S-W=.93, df=14, p=.568, Awake time during the night : S-W=.88, df=14, p=.309, Sleep latency : S-W=.98, df=14, p=.928, Immobile minutes : S-W=.90, df=14, p=.386, Immobile minutes %: S-W=.82, df=14, p=.118, Wake bouts: S-W=.85, df=14, p=.189, Mean Wake Bouts: S-W=.88, df=14, p=.314, Average Wake Movement: S-W=.95, df=14, p=.74, Fragmentation Index: S-W=.97, df=14, p=.84, IS: S-W=.914, df=14, p=.49, IV: S-W=.916, df=14, p=.507, Relative Amplitude: S-W=.84, df=14, p=.168

Maternal Report: Sleep time during the night: S-W=.71, df=16, p=.007, Sleep time during the day: S-W=.95, df=16, p=.729, Nighttime Awakenings: S-W=.92, df=16, p=.513, Wakefulness during the night (sleep latency): S-W=.92, df=16, p=.498, How long does it take to put your baby to bed: S-W=.92, df=16, p=.473, When does baby usually fall asleep for the night: S-W=.81, df=16, p=.076 Sleep time during the 24-hour period: S-W=.65, df=16, p=.001

Table 37: Descriptives of infant sleep at 5 months by maternal report

Infant Sleep (Maternal Report)	n=16	
	Mean (SD)	Range
Sleep time during the night (hh:min)	11:09 (01:07)	09:00-12:00
Sleep time during the day (hh:min)	02:28 (00:54)	01:30-5:00
Sleep time during the 24-hour period (hh:min)	13:35 (1:23)	11:30-15:00
Nighttime Awakenings (frequency)	3.09 (1.64)	1.00-5.50
Wakefulness during the night (sleep latency) (min)	33 (20)	8-90
How long does it take to put your baby to bed (min)	12 (2)	10-15
When does the baby usually go to sleep (clock time)	19:30 (00:52)	19:00-21:00
Do you consider your child's sleep a problem		
A serious one	4 (25%)	
A small one	7 (43.7%)	
Not a problem at all	5 (31.3%)	
Sleeping arrangement		
Infant crib in a separate room	6 (37.5%)	
Infant crib in parents room	5 (31.3%)	
In parents bed	1 (6.3%)	
Other	4 (25%)	
Position child sleeps in		
On belly	1 (6.3%)	
On side	7 (43.8%)	
On back	8 (50%)	

4.3.2.2 Associations between Maternal Depressive Symptoms and infant sleep as measured by actigraphy and questionnaire

Unadjusted bivariate associations were examined between maternal mental health as assessed on the EPDS and infant sleep in Table 38. Following normality tests the data on maternal depressive symptoms were not found to be normally distributed and so Spearman's two-tailed correlations were performed⁴⁴. No association was found between antenatal and postnatal depressive symptoms ($r_s=.155$, $p=.598$).

Actigraphy

No associations between antenatal maternal mental health and infant sleep as assessed through actigraphy emerged as significant (Table 38).

⁴⁴ Antenatal depressive symptoms S-W=.779, $df=17$, $p=.054$; Postnatal depressive symptoms S-W=.750, $df=17$, $p=.030$.

There was a consistent negative association between postnatal depressive symptoms and sleep duration. Postnatal depressive symptoms were associated with sleep duration during the 24-hour period, during the day and with the percentage of time spent sleeping during the night; suggesting shorter infant sleep duration when the mother reported a higher score on depressive symptoms. The association between postnatal depression and sleep duration over the night hours, although not significant was in the same direction.

There were also marginal positive associations between postnatal depression scores and total time spent in bed and infant's fragmentation index, suggesting more time spent in bed during the night and more fragmented sleep were associated with more depressive symptoms.

Questionnaire

An examination of mother-rated infant sleep revealed a significant association between antenatal mood and sleep during the day, suggesting that higher reported maternal depressive symptoms antenatally were associated with shorter daytime sleep duration. A similar trend was evident for sleep duration during the 24-hour period, although that might be expected given that the former variable was used to calculate the latter. The association between antenatal depression scores and sleep during the night although not significant was in the same direction.

Similarly to actigraphy-derived sleep duration, a trend was found for higher postnatal depressive symptoms being associated with shorter sleep duration during the 24-hour period.

A trend was also observed between the time the infant went to bed and postnatal depressive symptoms, with higher scores on depressive symptoms being associated with later times for going to bed.

Table 38: Unadjusted bivariate associations of maternal depressive symptoms in the antenatal and postnatal periods with infant sleep assessed through actigraphy.

Infant Sleep (Actigraphy)	Depressive Symptoms	
	Antenatal (n=14) rs (p)	Postnatal (n =14) rs (p)
Time in Bed	-.17(.586)	.50(.068)
Assumed sleep during the night	.23(.442)	.09(.755)
Actual Sleep time during the night	-.42(.151)	-.43(.128)
Actual sleep % during the night	-.36(.221)	-.53(.052)
Actual sleep time over the day	-.07(.821)	-.62*(.018)
Actual sleep time over the 24-hour period	-.08(.80)	-.59*(.026)
Awake time during the night	.03(.93)	.46(.537)
Sleep latency	-.02(.94)	-.13(.871)
Immobile minutes	-.5(.105)	.01(.988)
Immobile minutes %	-.37(.217)	-.03(.913)
Wake bouts	-.43(.148)	.02(.938)
Mean Wake Bouts	.35(.246)	.45(.111)
Fragmentation Index	.32(.289)	.51(.062)
IS	.21(.790)	.18(.540)
IV	-.84(.162)	.28(.655)
Relative Amplitude	-.42(.584)	.09(.755)

* $p < .05$, ** $p < .01$

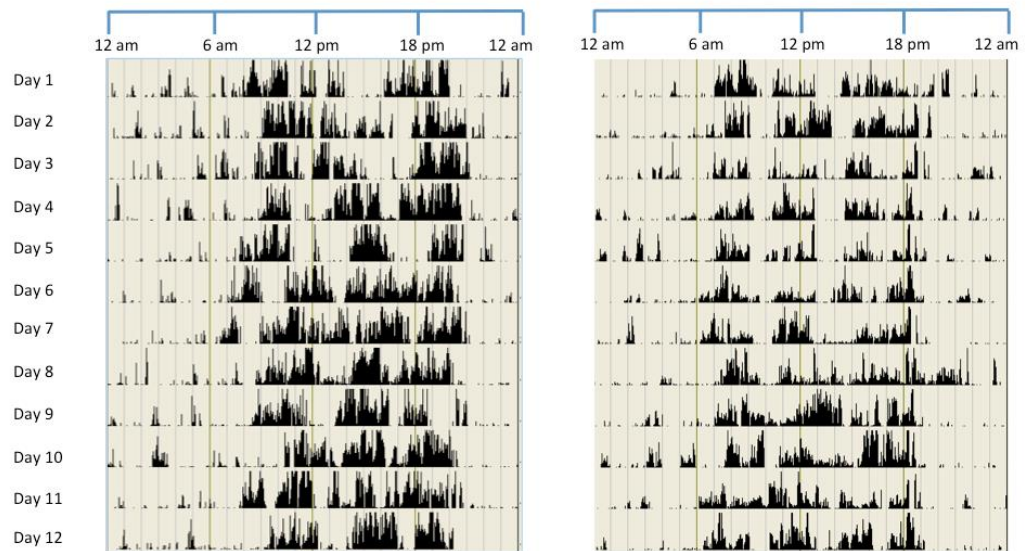
Table 39: Unadjusted bivariate associations of depressive symptoms in the antenatal and postnatal periods with infant sleep assessed through maternal report.

Infant Sleep (Questionnaire)	Depressive Symptoms	
	Antenatal (n=16) $r_s(p)$	Postnatal (n=16) $r_s(p)$
Sleep time during the night	-.40(.435)	-.37(.473)
Sleep time during the day	-.66*(.028)	-.67(.148)
Sleep time during the 24-hour period	-.77(.072)	-.75(.084)
Nighttime Awakenings	.09(.862)	-.13(.803)
Wakefulness during the night	.71(.118)	-.47(.346)
How long does it take to put your baby to bed	-.31(.546)	-.22(.682)
When does baby usually go to sleep	.32(.541)	.53(.081)

* $p < .05$, ** $p < .01$

There was an overall negative association between sleep duration and both ante- and postnatal maternal depressive symptoms, suggesting that higher depressive symptoms were associated with shorter sleep duration with a stronger association evident for sleep during the day time. Maternal depressive symptoms were not found to be associated with nighttime sleep parameters, with the exception of lower actual sleep % (between sleep start and sleep end), and a higher fragmentation index indicating more activity at night.

Figure 14: Single plotted actogram of 11 days recorded from two infants 5 months postpartum. Rest-activity is entrained to the day-night cycle at 5 months but inter-individual differences in bed times are already evident (left actogram on average 21:00 and right actogram on average 18:30)



4.3.2.3 Associations between infant actigraphy and maternal report of infant sleep

This section examines the inter-correlations between i) actigraphy variables, ii) questionnaire variables and iii) the agreement between infant sleep as assessed through actigraphy and maternal report. For this latter aim associations are only examined for variables, which correspond in actigraphy and maternal report to avoid multiple testing.

Actigraphy

Associations between infant sleep variables through actigraphy are presented in Appendix 40, page 326. Large coefficients were observed in so-called ‘inter-related variables’, which are calculated using some of the other parameters included, for example percentage of sleep during the night was strongly negatively correlated with time spent awake during the night and mean time of wake bouts ($r=-.78, p=.001$ & $r=-.67, p=.006$).

A number of significant associations emerged from this analysis in the expected direction.

Similarly, sleep duration over night was associated with average immobile minutes and average immobile time (%) ($r=.86, p=.056$ and $r=.87, p=.058$ respectively); time spent awake during the night was positively associated with mean wake bout time $r=.84, p=.019$. Associations were also evident between infant fragmentation index and sleep % during the night, awake time during the night and mean wake bout time as these variables are used to calculate the fragmentation index ($r=-.76, p=.012, r=.62, p=.028$, & $r=.78, p=.002$). Finally, the relative amplitude was associated with sleep time and sleep % over night, and with wake bouts and mean wake bout time ($r=.49, p=.042, r=.51, p=.034, r=-.67, p=.006, r=-.56, p=.008$).

Questionnaire

Appendix 41 presents unadjusted bivariate associations for infant sleep variables as assessed through maternal report.

It was hypothesized that sleep time during the day would be negatively associated with sleep during the night with infants sleeping less overnight compensating with sleep during the day and positively associated with wakefulness over the night, with infants who spent longer being awake during the night sleeping more during the day. The first

hypothesis was not confirmed in this sample. Sleep during the day was associated with wakefulness during the night with infants who exhibited more wakefulness during the night also sleeping longer during the day confirming the second hypothesis ($r=.57$, $p=.022$).

It was further hypothesized that sleep onset would be negatively associated with sleep during the night, with infants going to bed later sleeping less overall during the night. This hypothesis was not confirmed in this study ($r=-.48$, $p=.302$).

A significant association emerged for sleep duration over the night and over the 24-hour period. This is not surprising, as the latter variable is the sum of sleep duration over the night and over the day ($r=.76$, $p=.046$).

Finally, section 4.3.2.2 presents unadjusted associations between infant sleep variables assessed through maternal report and actigraphy to examine the agreement between subjective and objective reports in this sample. High agreement rates were expected for sleep onset and night awakenings in accordance with findings by Sadeh (2004a) when using this measure.

High coefficients were observed for almost all variables although only sleep onset emerged as significant ($r=.91$, $p=.03$).

Table 40: Unadjusted bivariate associations between sleep variables as measured by actigraphy and maternal report (n=14).

		Maternal Report					
		Sleep time during the night	Sleep time during the day	Sleep time during the 24- hour period	Nighttime Awakenings	Wakefulnes s during the night	When does baby usually go to sleep
Actigraphy	Actual Sleep time during the night	.63(.259)					
	Actual sleep time over the day		.79 (.116)				
	Actual sleep time over the 24-hour period			.76 (.107)			
	Wake bouts				.62 (.262)		
	Awake time during the night					.22 (.729)	
	Sleep Start						.91* (.030)

4.3.3 Analysis of Secondary outcomes

4.3.3.1 Associations between Maternal Cognitions about Sleep and Infant Sleep

The table below presents the descriptives for maternal cognitions about sleep (Table 41). Associations between cognitions relating to maternal sleep and maternal depressive symptoms are presented in Table 42. The data were normally distributed with the exception of the Safety dimension⁴⁵. Spearman's rho correlations were used.

Postnatal maternal depressive symptoms were marginally associated with cognitions about feeding, higher scores on the EPDS were associated with cognitions referring to the importance of feeding for soothing and worries about the child going hungry during the night.

Table 41: Descriptives for maternal cognitions.

	<i>n</i> =16	
	Mean (SD)	Range
Limit Setting	15.44(6.59)	6-24
Anger	6.56(3.20)	3-11
Doubt	8.06(4.73)	9-14
Feeding	4.44(3.50)	0-9
Safety	2.56(2.92)	0-7
Total Scale	37.06(17.29)	13-58

⁴⁵ Limit setting: S-W=.85, df=16, p=.132, Anger: S-W=.94, df=16, p=.614, Doubt: S-W=.93, df=16, p=.554, Feeding: S-W=.97, df=16, p=.91, Safety: S-W=.70, df=16, p=.004 Total Score: S-W=.97, df=16, p=.895.

Table 42: Unadjusted bivariate associations between maternal cognitions and depressive symptoms.

	Limit Setting	Anger	Doubt	Feeding	Safety	Total
Depressive Symptoms <i>n</i> =16, <i>r_s</i> (<i>p</i>)						
Antenatal	-.27(.610)	-.33(.525)	-.53(.275)	.40(.427)	-.22(.675)	-.10(.849)
Postnatal	-.39(.441)	.06(.906)	.22(.680)	.79(.059)	.44(.258)	.13(.813)

Associations between maternal cognitions and sleep were also examined. The findings are presented in Appendix 42.

Actigraphy

Moderate correlations in actigraphy-derived sleep variables emerged between Limit Setting and sleep latency suggesting that parents experiencing more difficulties with resisting infant demands or responding to those demands, had infants who took longer to fall asleep ($r=-.56$, $p=.011$). Additionally, maternal doubt was associated with Intra-daily Variability suggesting that parents who reported more doubts or uncertainty as to whether their parenting was adequate had infants who displayed more intra-daily variability ($r=.59$, $p=.042$). A trend was also present between feeding and sleep during the day ($r=-.46$, $p=.061$).

Questionnaire

Analysis of variables from mother-rated sleep questionnaires revealed the following associations: Nighttime awakenings were associated with Limit Setting (trend, $r=.69$, $p=.086$), doubt ($r=.78$, $p=.037$) and maternal cognitions total score ($r=.87$, $p=.011$) suggesting that a higher number of nighttime awakenings was associated with maternal difficulties of resisting infant demands and parental uncertainty as to whether their parenting was adequate. Limit Setting was also associated with sleep duration overnight ($r=-.76$, $p=.046$) suggesting shorter sleep duration for infants of mothers reporting difficulties with resisting infants' demands. How long it took parents to put infants to sleep was associated with anger, doubt and the total score ($r=.74$, $p=.058$, $r=.89$, $p=.006$, & $r=.69$, $p=.086$) suggesting that the longer it took parents to settle infants in bed the higher their potential feelings of anger or regret and uncertainty about their parenting.

4.3.3.2 Associations between Maternal Depressive Symptoms and Temperament

Table 43 presents the descriptives for infant temperament⁴⁶. Unadjusted bivariate associations for temperament and maternal depressive symptoms were examined and are presented in Table 44. No association was found between ante- or postnatal depressive symptoms and infant temperament scores.

Table 43: Descriptives for infant temperament scores.

	<i>n</i> =16	
	Mean (SD)	Range
Infant Temperament		
Activity	3.91(0.76)	2.94-5.18
Smile	5.06(0.68)	4.29-6.79
Novelty	2.36 (0.62)	1.69-4.08
Distress	3.67(1.3)	1.84-5.00
Soothability	5.28(1.11)	4.44-7.00
Duration of Orienting	3.49(0.71)	2.64-5.22

Activity: S-W=.96, df=16, p=.847, Smile: S-W=.97, df=16, p=.924, Novelty: S-W=.89, df=16, p=.308, Distress: S-W=.82, df=16, p=.066, Soothability: S-W=.83, df=16, p=.080, Duration of Orienting: S-W=.95, df=16, p=.864

Table 44: Unadjusted bivariate associations between maternal depressive symptoms and infant temperament

	Activity	Smile and Laughter	Novelty	Distress	Soothability	Duration of Orienting
Antenatal Depressive Symptoms	-.20(.698)	-.39(.433)	-.48(.333)	.41(.414)	-.64(.168)	-.32(.525)
Postnatal Depressive Symptoms	.46(.349)	-.19(.714)	-.22(.665)	.27(.597)	-.44(.377)	-.20(.700)
Activity	—	.31(.487)	.37(.409)	.50(.244)	-.20(.664)	.24(.601)
Smile and Laughter		—	.79*(.036)	.18(.700)	.34(.454)	.78*(.037)
Novelty			—	.19(.675)	.64(.115)	.66**(.001)
Distress				—	-.56(.190)	.31(.498)
Soothability					—	.56(.192)
Duration Orienting	of					—

*p<.05, **p<.01

4.3.3.3 Maternal and Infant Cortisol

4.3.3.3.1 Descriptives

The following table displays the descriptive statistics for maternal and infant cortisol levels.⁴⁷ The data is also presented in Figure 15.

Table 45: Descriptives for infant cortisol at 5 months of age and maternal cortisol ante- and postnatal.

	Infant Cortisol			Antenatal maternal cortisol			Postnatal maternal cortisol		
	n	Mean (SD)	Range	n	Mean (SD)	Range	n	Mean (SD)	Range
Sample 1	15	4.74(1)	3.00-5.60	11	7.68(.37)	7-7.9	12	4.7(.92)	3.7-5.7
Sample 2	15	5.79(1.72)	3.60-7.90	12	10.62(2.09)	9.5-14.7	15	7.2(2.49)	4-10.1
Sample 3	15	4.63 (2.03)	2.20-7.60	12	11.6(2.43)	10.10-15.7	14	7.74(3.79)	2.2-11.1
Sample 4	15	3.16(1.07)	1.30-4.50	11	11.42(1.06)	10-12.1	15	8.31(4.85)	2.10-20.1

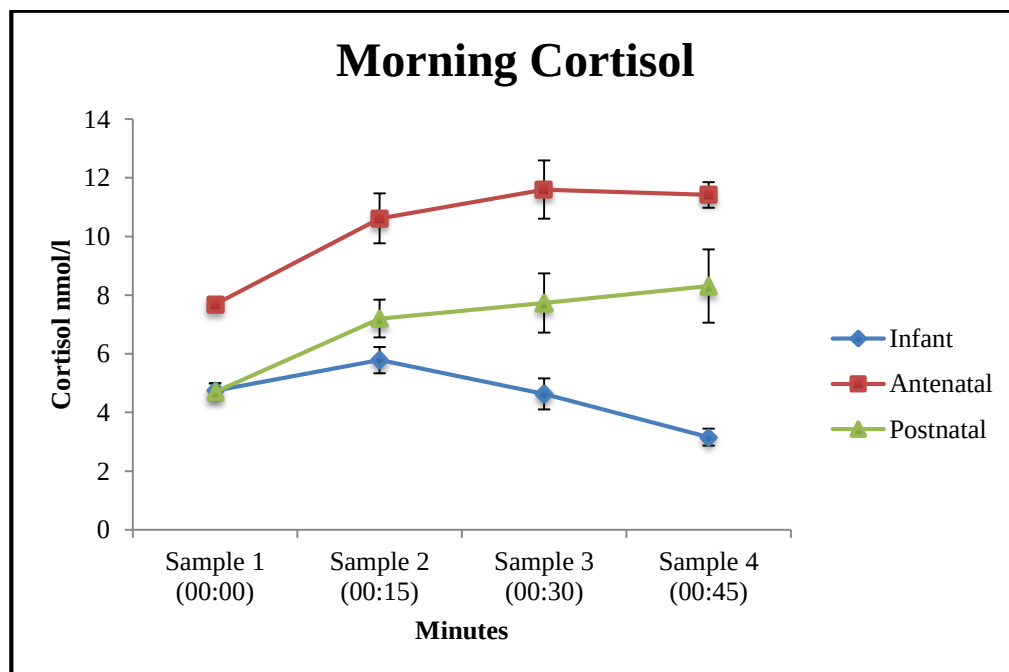


Figure 15: Maternal antenatal, postnatal and infant morning cortisol levels.

⁴⁷ Sample 1: S-W=.86, df=15, p=.183, Sample 2: S-W=.86, df=15, p=.195, Sample 3: S-W=.92, df=15, p=.536, Sample 4: S-W=.92, df=14, p=.554

4.3.3.3.2 Associations between Maternal Depressive Symptoms and Maternal and Infant Cortisol

Table 46 presents associations between infant cortisol samples and maternal depressive symptoms (Spearman's rho). No associations emerged as significant.

Table 46: Unadjusted bivariate associations maternal depressive symptoms and infant cortisol.

(n=15)	Infant Cortisol			
	Sample 1	Sample 2	Sample 3	Sample 4
Antenatal Depressive Symptoms	-.43(.465)	-.63(.259)	-.43(.467)	-.70(.301)
Postnatal Depressive Symptoms	-.29(.634)	.22(.728)	.69(.202)	.78(.119)
Cortisol				
Sample 1	—	.51(.297)	-.56(.253)	.11(.858)
Sample 2		—	.23(.663)	.74(.153)
Sample 3			—	.85*(.046)
Sample 4				—

* $p < .05$

4.3.3.4 *Maternal Sleep ante- and postnatally*

Table 47 presents the descriptives for maternal sleep as assessed through the PSQI and actigraphy. Differences were examined using repeated measures tests; Wilcoxon Signed Ranked tests for the questionnaire data and paired sample t-tests for actigraphy data.

Regarding, questionnaire data, a marginal difference was found for sleep latency ($T=6$, $p=.083$) with sleep latency scores being higher in the postnatal period suggesting it took participants longer to fall asleep. This trend was confirmed in actigraphy data. Significant differences emerged for most actigraphy-derived sleep variables. Participants in the postnatal period spent less time sleeping during the night and less total time in bed (compared to the antenatal period). Latency periods were slightly longer in the postnatal period and a higher percentage of the night was spent immobile. As expected participants in the postnatal period exhibited more wake bouts, interestingly though the mean wake bout time was slightly shorter in the postnatal compared to the antenatal period. During the antenatal period participants exhibited a higher fragmentation index, a lower inter daily stability and a higher intra-daily variability. To further illustrate the differences in actigraphy variables they are also presented graphically in Figure 16.

Figure 16 presents actigraphy data from two mother-infant dyads ante- and postnatally to illustrate i) changes in sleep ante-and postnatally and ii) the paired mother-infant activity/rest patterns.

Table 47: Descriptives for maternal antenatal and postnatal sleep as assessed through the PSQI and actigraphy.

			Antenatal (n=15)		Postnatal (n=16)		Statistic
			Median	Range	Median	Range	Wilcoxon-Signed Rank Test
Maternal PSQI	Subjective Sleep Quality		1	1-3	2	1-3	T=0, p=.157
	Sleep Latency		2	1-3	1	0-2	T=6, p=.083
	Sleep Duration		0	0-3	1	0-2	T=2.5, p=.317
	Habitual Sleep Efficiency		1	0-3	1.5	0-3	T=5, p=.285
	Sleep Disturbances		1	1-2	2	1-3	T=1.5, p=.414
	Use of sleeping Medication		0	0	0	0-0	no use of sleeping medication ante or postnatally
	Daytime Dysfunction		1	0-2	1	0-1	T=6, p=.109
	Total PSQI Score		7	4-15	8	5-13	T=3, p=.450
			(n=13)		(n=15)		Paired sample t-test
			Mean (SD)	Range	Mean (SD)	Range	
Actigraphy	Time In bed (hh:min)		09:16(00:07)	06:47-09:32	08:57(00:18)	08:15-09:42	t(12)=3.42, p=.005**
	Actual sleep time (hh:min)		07:30(00:11)	05:07-07:45	07:08(00:13)	06:47-07:51	t(12)=4.56, p=.001**
	Actual sleep (%)		81.87(02.58)	79.61-85.34	81.34(01.18)	79.45-85.12	t(12)=1.06, p=.311
	Sleep latency (min)		00:10(00:00)	00:09-00:18	00:11(00:05)	00:09-00:30	t(12)=-2.35, p=.039*
	Immobile minutes (min)		293.71(205.86)	16.00-453.26	425.22(10.28)	401.31-478.38	t(12)=-2.19, p=.051
	Immobile time (%)		63.85(29.92)	23.36-85.05	84.29(00.56)	78.25-85.05	t(12)=-2.39, p=.036*
	Wake Bouts		21.51(15.00)	00.00-40.50	32.71(03.52)	23.73-37.43	t(12)=-1.90, p=.084
	Mean Wake Bout Time (min)		00:07(00:03)	00:02-00:11	00:02(00:00)	00:02-00:03	t(12)=4.36, p=.001**
	Fragmentation Index		47.28(11.33)	39.15-62.61	31.54(0.58)	30.78-41.01	t(12)=4.59, p=.001**
	IS average		0.50(0.19)	0.31-0.74	0.67(0.05)	0.52-0.72	t(12)=-2.82, p=.017*
	IV average		0.86(0.13)	0.69-0.96	0.68(0.04)	0.55-0.86	t(12)=7.14, p=.000**
	Relative Amplitude		0.79(0.11)	0.68-0.94	0.87(0.04)	0.82-0.92	t(12)=-2.83, p=.015*

*p<.05, **p<.01

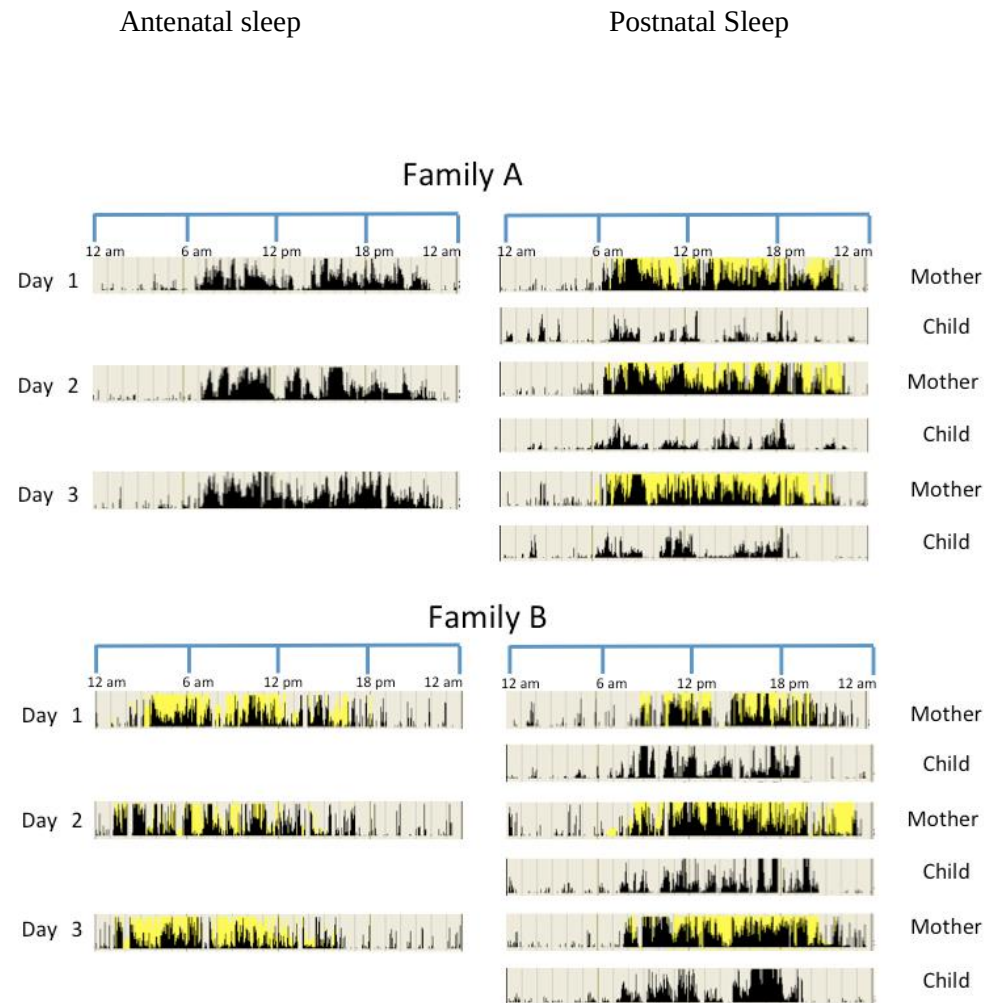


Figure 16: Single plotted actograms of two mother-infant dyads 5 months postpartum.

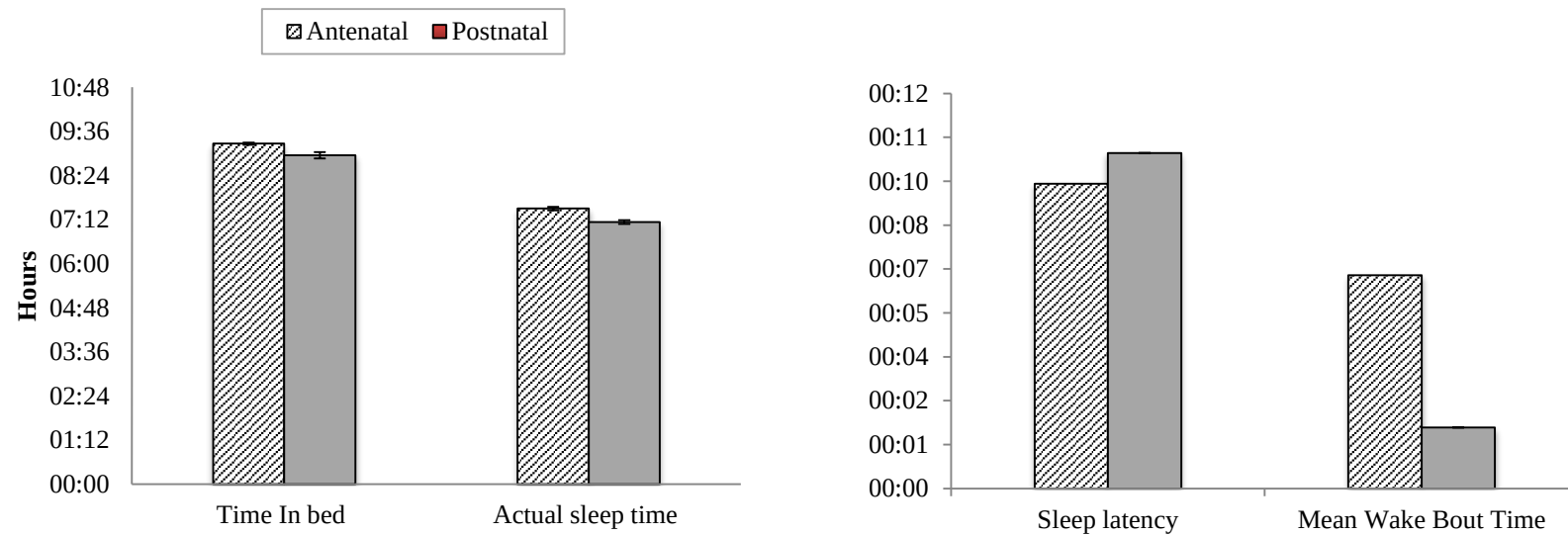


Figure 17: The mean ($\pm$ SE) values for all sleep parameters in the antenatal (striped column) and postnatal periods (solid columns) as assessed by actigraphy, paired-samples *t*-tests, * $p < .05$

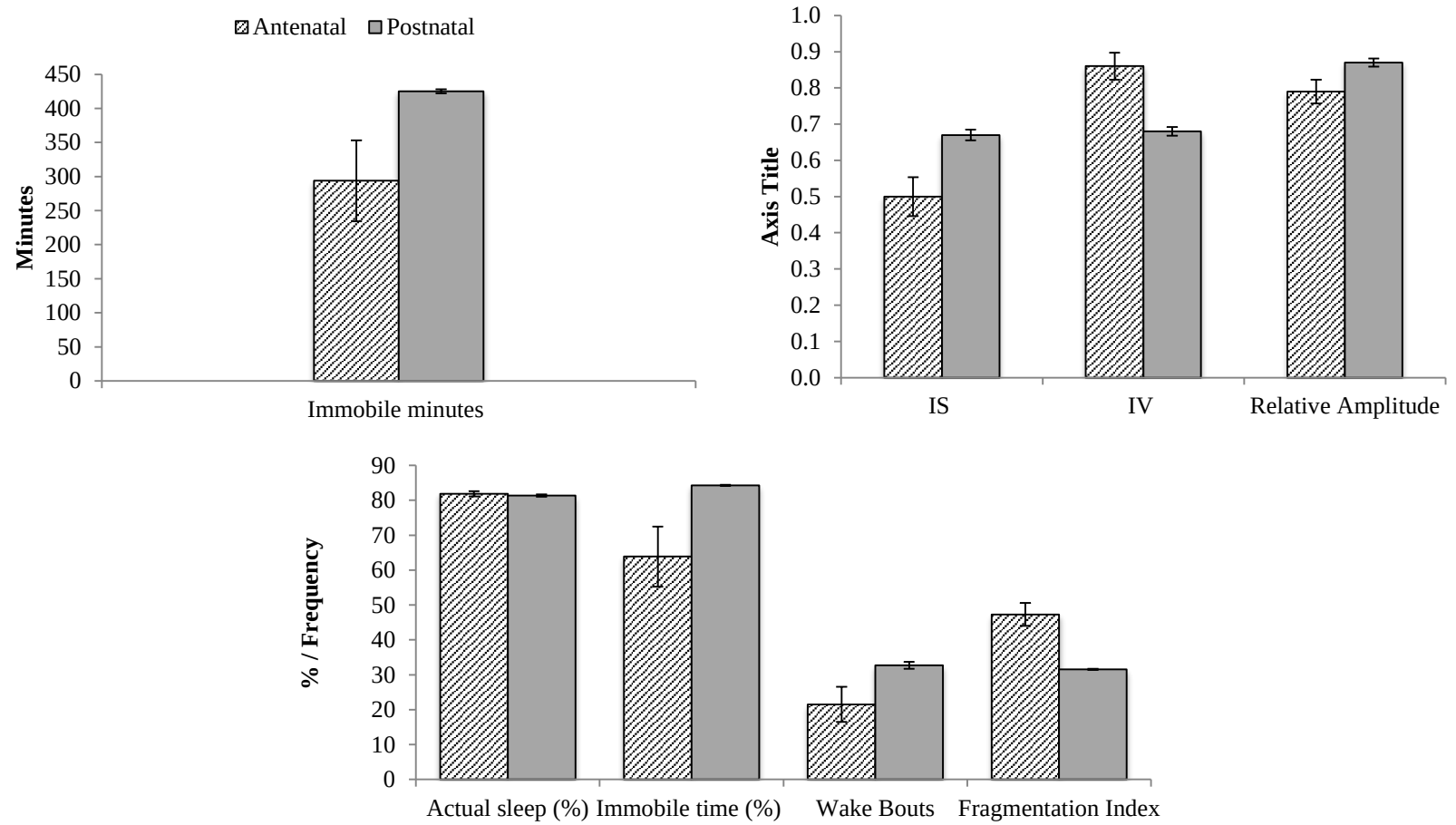


Figure 17 (continued): The mean ($\pm$ SE) values for
all sleep parameters in the antenatal (red striped) and postnatal periods (solid columns) as assessed by actigraphy, paired-samples t -tests, $*p < .05$

4.3.3.4.1 Associations between maternal sleep and depressive symptoms

Table 14 presents associations between maternal sleep variables and depressive symptoms. Antenatal depressive symptoms were associated with postnatal immobile minutes and fragmentation index. Postnatal depressive symptoms were associated with the fragmentation index and with Relative Amplitude in the postnatal period and with immobile minutes and % of immobile minutes in the antenatal period.

Table 48: Unadjusted associations between antenatal and postnatal maternal sleep

		Antenatal Maternal Depressive Symptoms	Postnatal Maternal Depressive Symptoms
		r(s)	r(s)
PSQI	Global PSQI Score – Antenatal	-0.04(.935)	0.71(.184)
	Global PSQI Score – Postnatal	-0.34(.582)	-0.12(.848)
	Time In bed	0.89(.106)	0.63(.368)
Antenatal Actigraphy	Actual sleep time	0.45(.553)	-0.32(.684)
	Actual sleep (%)	0.67(.329)	-0.16(.843)
	Sleep latency	-0.57(.434)	-0.42(.580)
	Immobile minutes	-0.33(.667)	-0.44(.063)
	Immobile time (%)	-0.52(.482)	-0.45(.051)
	Wake bouts	-0.19(.813)	0.65(.351)
	Mean wake bout	0.24(.764)	0.33(.667)
	Fragmentation index	-0.39(.106)	-0.61(.391)
	IS	0.02(.981)	-0.71(.291)
	IV	-0.52(.483)	0.34(.657)
	Relative Amplitude	0.39(.614)	-0.20(.799)
Postnatal Actigraphy	Time In bed	0.22(.718)	0.21(.741)
	Actual sleep time	0.66(.223)	0.10(.873)
	Actual sleep (%)	0.67(.215)	-0.30(.624)
	Sleep latency	-0.34(.571)	0.36(.553)
	Immobile minutes	0.40* (.040)	-0.15(.816)
	Immobile time (%)	-0.25(.684)	-0.70(.188)
	Wake bouts	-0.41(.488)	0.20(.747)
	Mean wake bout	-0.15(.813)	0.45(.450)
	Fragmentation index	0.39* (.041)	0.40* (.037)
	IS	0.45(.445)	-0.23(.710)
	IV	-0.64(.248)	0.26(.671)
	Relative Amplitude	0.18(.774)	-0.33(.081)

* $p < .05$, ** $p < .01$

Summary of Findings

- i. Recruitment in this population group proved more challenging than anticipated despite trying different recruitment strategies over an extended period of time.
- ii. Antenatal depressive symptoms were associated with shorter sleep duration as reported by maternal report though there was no strong evidence found of an association using actigraphy measurement during the day.
- iii. A consistent association between postnatal depressive symptoms and shorter sleep duration was found as assessed by both actigraphy and maternal report.
- iv. High agreement between actigraphy and maternal report were evident for several sleep characteristics.
- v. No associations were found between antenatal or postnatal depressive symptoms and:
 - a. Maternal cognitions about sleep
 - b. Infant temperament
 - c. Infant cortisol
- vi. Differences were evident in antenatal and postnatal sleep on most actigraphy variables although this was not reflected on maternal report of sleep.
- vii. Antenatal depressive symptoms were associated with maternal postnatal immobile minutes and fragmentation index.

4.4 DISCUSSION

4.4.1 The findings

Primary Findings

It was hypothesized that antenatal depression would be associated with shorter sleep duration, higher number of night awakenings and longer wakefulness in infants during the night. Antenatal depression was associated with shorter infant sleep duration using maternal report. There was no association between antenatal depressive symptoms and actigraphy derived variables or any other mother-rated infant sleep variables. The finding that antenatal depressive symptoms were associated with maternal reports of shorter sleep duration is in line with three previous studies using actigraphy and maternal reports (Armitage, et al., 2009; Armstrong, et al., 1998; Nevarez, et al., 2010). This study provides further evidence that a multitude of factors contribute to disturbed sleep and that monitoring maternal mental health from the antenatal period and providing care is important for both mothers and babies. The finding of a stronger effect for the group receiving CBT treatment suggests that addressing maternal mental health during pregnancy may have beneficial effects for child development. The exact mechanisms remain unclear however, it is possible that improvement in maternal depressive symptoms may lead to a mother's increased sense of confidence in dealing with a young baby and to improved mother-infant interaction.

One of the key biological mechanisms implicated in the transmission of risk from mother to child stipulates that increased production and transfer of glucocorticoids from the mother to the fetus has the potential to alter the programming of the HPA axis. In animal research a number of studies suggest altered circadian rhythmicity in antenatally stressed rats leading to increased sleep fragmentation and increased REM sleep (Dugovic, et al., 1999; Maccari, et al., 2003). Due to the small sample size it was not possible to control for confounders. Two factors are of particular importance maternal age and socioeconomic status as they have been both associated with antenatal depression and with sleep duration in children. For example, children of mothers over 35 years of age were reported to sleep less, whereas children of young mothers <21 years slept longer and children from lower socioeconomic groups went to bed later and woke up later (Baird, et al., 2009).

Shorter sleep duration in infants was also associated with postnatal depressive symptoms, when using both objective (actigraphy) and subjective (mother-rated) measures of infant sleep. Surprisingly, no association was found between antenatal depressive symptoms and awakenings. This is contrary to many studies including the ones discussed in this thesis (Chapter 2,3), where high correlations were found (O'Connor, et al., 2003).

There was a high agreement rate in sleep onset between objective and subjective measures, as found in previous work (Sadeh, 2004b). Agreement was also evident in other sleep parameters although these associations did not reach statistical significance. The absence of statistically significant associations despite the correlations of high magnitude may be attributed to the small sample size of the study, which is discussed in more detail in the limitations section below.

Secondary Findings

There was no association between antenatal depressive symptoms and maternal cognitions about sleep. There was a strong association however between postnatal depressive symptoms and the feeding parameter, suggesting that higher depressive symptoms were associated with beliefs about the importance of feeding to soothe the infant and worries about the child going hungry during the night.

There were no associations between infant temperament and antenatal or postnatal depressive symptoms. There were also no associations between infant cortisol and antenatal or postnatal depressive symptoms. The absence of an association between antenatal depression and maternal cognitions about sleep, infant temperament and infant cortisol were unexpected given the large body evidence suggesting otherwise. Here again the small sample size may have been a key reason for the absence of an association. First, this would result in a lack of statistical power to detect differences between groups and second, to a low variability in depression scores and in maternal cognition scores, temperament and cortisol scores. Particularly with respect to depression scores the sample did not score high on depressive symptoms indicating a low severity level in this group. An additional reason for the lack of an association relevant to infant cortisol is the choice of measurement i.e. morning cortisol. The studies discussed in the Introduction section (p.175) used diurnal levels of cortisol or cortisol

reactivity in response to a stress task. A substantial issue with measuring morning cortisol is that participants have to collect the samples themselves introducing a number of potential errors for example, not collecting the sample at the right intervals, not following guidelines regarding eating prior to collection and storage of samples until collection. In this study mothers collected the cortisol samples and in 5 cases antenatally and 4 postnatally did not collect enough saliva or did not store it properly, which further limited the sample size.

Analysis of antenatal and postnatal maternal sleep revealed differences in most sleep parameters including longer sleep time and longer wake bouts, a higher fragmentation index, lower intra-daily stability and a higher intra-daily variability antenatally. These differences were not reflected in self-reported sleep parameters. In analysis of antenatal vs. postnatal maternal sleep many differences emerged as significant in the actigraphy variables but not in the questionnaire measures this might suggest that although sleep does change from one time point to the other the perception and subjective quality of sleep are not altered. These changes are in the expected direction according to previous literature.

Antenatal sleep, and more specifically, fewer minutes spent immobile was associated with postnatal depressive symptoms but not with concurrent antenatal depressive symptoms. Postnatal immobile minutes and fragmentation index were associated with antenatal and postnatal depressive symptoms.

This study attempted to include information on fathers. There is a dearth of research on this topic particularly with how fathers' sleep is affected and what the paternal contribution to disturbed infant sleep is. It was surprising to observe that in the daily diaries no activity for infants indicated as taking place with the father. This could be because at this early stage of development fathers have little involvement. Alternatively mothers may have omitted this information, as they may have thought that only information relating to maternal and infant sleep was relevant. There is a known difficulty in research with fathers, however the lack of knowledge of their contribution may be critical in understanding more about infant sleep (Loutzenhiser & Seigniny, 2008).

4.4.2 Strengths and Limitations

This was the first study to our knowledge to collect objective long term recordings of both maternal and infant sleep, in conjunction with subjective data. To my knowledge, only one previous study had examined infant sleep using objective measurement in the context of maternal depressive symptoms (Armitage, et al., 2009).

A potential strength of this study is that mothers were aware that the main focus of the study was theirs and their baby's sleep. Completing the diaries everyday may have inclined them to be more focused on this aspect of the child's behaviour and they may have been more accurate in their reporting, as they may have been more thoughtful in their response. This would be in contrast to larger cohort studies such as the ones described in Chapters 2 and 3 where mothers were given large questionnaires enquiring about all aspects of development and sleep would have been a small part of that.

The main limitation of this study was the challenges faced with recruitment, which resulted in a smaller sample than anticipated. Different recruitment strategies were attempted which had proven successful in other studies recruiting this population group. As discussed earlier, several explanations as to why these difficulties were encountered have been identified. This study has given valuable information regarding how to design large-scale studies using this population group. More recent studies taking place in our group have utilized social media and meeting spots for pregnant women for example, centres hosting antenatal classes.

The study was designed based on power calculations in order to detect effect sizes of 0.8. Despite the small sample size, this study has the opportunity to provide preliminary exploratory evidence that may inform future research. For this reason, the consistency of findings was highlighted with a lesser focus on statistical significance achieved as this may have been due to low numbers. It follows, that many of the findings here may not withstand Bonferroni correction and until further replication findings should be interpreted with caution.

Due to the small sample size it was not possible to examine how siblings in the home may affect both the sleep of the mother and the study baby. It can be hypothesised that awakenings from siblings would disrupt both the mother's and baby's sleep leading to more awakenings and wakefulness during the night. Particularly with maternal sleep and how added night-time disturbances may contribute to depressive symptoms, first

time mothers in a sample of depressed participants have been reported to have worse sleep compared to multipara women with respect to sleep efficiency and wakefulness during the night as measured by actigraphy (Dørheim, Bondevik, Eberhard-Gran, & Bjorvatn, 2009). Future studies should further investigate these associations.

Due to the small sample size it was not possible to control for a number of known confounders for example, maternal age, infant sex and postnatal depressive symptoms (Bartels, de Geus, Kirschbaum, Sluyter, & Boomsma, 2003). Nevertheless this sample was homogeneous in terms of ethnic background, a variable that was already shown to confound results relating to infant sleep in Chapter 2. This would suggest that results presented here may be generalizable in this population group.

4.4.3 Future research

This pilot study has provided with valuable information regarding recruitment of this population group. In future, studies should attempt to widen their recruitment methods and include social media, NCT classes and other meeting places for pregnant women for example, yoga classes and swimming clubs. Despite the small sample size this study has suggested that antenatal depressive symptoms are associated with maternal reports of sleep but not with objective measures (actigraphy). Large-scale studies are needed in order to replicate these findings and to further understand the association between antenatal depression and infant sleep. Future studies should also attempt to include paternal assessments of their sleep and of infant development to assess paternal contribution to the development of infant sleep rhythms.

In conclusion, this was an exploratory pilot study of infant sleep in the context of antenatal maternal depressive symptoms. This research has highlighted important feasibility issues for future research and has provided evidence to suggest that antenatal depression is associated with infant sleep. This research has also emphasized the importance of a relatively understudied variable, maternal sleep, which may be important in delineating the mechanisms through which antenatal depression confers risk to infant sleep. Large-scale studies are needed to further understand this complex association and whether antenatal depression has a causal role in disturbed infant sleep.

Chapter 5: A pilot randomized
controlled trial of cognitive
behavioural therapy for women with
antenatal depression; infant
outcomes

5 Chapter Overview

The previous chapters addressed two key questions about the association between antenatal depression and infant sleep: are some individuals disproportionately affected by antenatal depression, and is the association confirmed when more objective measures are used. Evidence that antenatal depression is associated with detrimental child outcomes, specifically infant sleep, has already been presented. The next step in further understanding the association between antenatal depression and infant development is to examine how treatment of depressive symptoms impacts on infant development. It remains to be established whether this may be an association of cause and effect. In order to determine this it is critical to move beyond observational epidemiological studies to experimental designs such as randomised controlled trials.

This chapter discusses evidence from a pilot randomized controlled trial for women with antenatal depression. Women were randomly allocated to Cognitive Behavioural Therapy (CBT) or Care as Usual, during the first trimester of pregnancy. This chapter focuses on the assessments of infant temperament and sleep at 2 months of age. This is the first study to report on infant outcomes following an RCT for antenatal depression.

5.1 INTRODUCTION

This thesis has already discussed potential moderators of the association between antenatal depression and infant sleep and the different methodologies used to assess sleep in young infants. Having already established the association between antenatal depression and infant sleep in this and other studies it is important to investigate potential mechanisms and the potential reversibility of these effects through manipulation of these mechanisms. To date, all published studies have been observational in nature and to a certain extent have informed us on the temporal order of risk (antenatal depression) and outcome (infant sleep). However, this is still some way short of establishing a causal association. Through experimental designs such as Randomised Controlled Trials (RCT) it is possible to identify the mechanisms which place infants of depressed mothers at risk.

This study is a pilot RCT of women with antenatal depression who received either Cognitive Behavioural Therapy (CBT) or Care as Usual. This is the first trial for antenatal depression to examine child outcome. RCTs such as this one have the potential to provide clear and unbiased evidence of the effect of a certain intervention and are the ideal methodological design to establish this in the case of antenatal depression (Prince, Stewart, Ford, & Hotopf, 2003). Research of animals has already demonstrated the reversibility of stress effects through careful manipulation of animal stress levels during pregnancy and cross-fostering of offspring (Weaver et al., 2004), but this has not been examined in humans. The present trial was conducted at Bristol University, UK (Principal Investigator: Dr Jonathan Evans). Myself and one of my supervisors (PR) contributed to the design of the study in part by selecting the child outcomes.

Examining the effect of treatment of depression on child development is the next step in unravelling the complex association between antenatal depression and child development. An RCT is a unique methodological opportunity to do so. Although this pilot trial was not powered to provide an estimate of the effect of treatment on child outcome, it presents as an ideal exploratory study for preliminary evidence in this field.

Interventions for the treatment of depression during pregnancy, though currently limited, are important for the following reasons. First, they have the potential to improve

maternal well being. Research by Flynn and colleagues (2006) suggest that only half of the women suffering from perinatal depression receive treatment.

Second, untreated antenatal depression has also been documented as a risk factor for postnatal depression. A study of 417 pregnant women in the UK reported that 22.6% of those suffering from antenatal depression went on to develop postnatal depression (Johanson, Chapman, Murray, Johnson, & Cox, 2000; Josefsson, Berg, Nordin, & Sydsjö, 2001) and a study of 1,489 pregnant women reported that 45% of those experiencing depression in the postnatal period had also suffered from antenatal depression (Evans, et al., 2001). Treatment of antenatal depression, therefore, may in some cases prevent postnatal depression. This in turn may prevent known interruptions to mother-infant interaction, attachment and maternal responsiveness, all of which have been shown to affect later development (Murray, Creswell, & Cooper, 2009; Stein et al., 2012). Antenatal depression has also been shown to affect maternal responsiveness and this association was independent of postnatal depression, thus further highlighting its potential impact on child development (Pearson, et al., 2012).

Third, women suffering from depression during pregnancy are more likely to smoke and drink alcohol, which have been shown to independently affect long-term fetal and infant development. Improvement in maternal mood may decrease the frequency of such behaviours, thereby indirectly promoting infant development (Barr, et al., 2006).

Finally, timely interventions may reverse or prevent negative effects on fetal development. Although there is limited research on the effects of treatment of antenatal depression on infant development, animal research, where extensive experimental manipulation is possible, has suggested that this may be possible (Weaver, et al., 2004).

Pregnancy is an optimal period for detecting and helping individuals suffering from even mild to moderate symptoms of depression, due to frequent interaction with health practitioners. Treatment of depression during pregnancy, however, requires a different consideration to treatments available during other periods of life, due to the currently limited knowledge on the effect of antidepressants on the developing fetus and to the lower acceptability of pharmacological treatment during this period (Freeman, 2007). A number of studies suggest an increased risk of cardiac malformations, persistent pulmonary hypertension and low birth weight, amongst others, although the evidence is not well documented and many studies suffer from significant methodological

limitations, including small sample sizes and un-blinded investigators (Fenger-Grøn, Thomsen, Andersen, & Nielsen, 2011). A recent investigation of SSRI use in the Generation R cohort with respect to birth outcomes suggested that untreated antenatal depression was associated with reduced fetal body and head growth (El Marroun et al., 2012). Antenatal exposure to SSRI use was not associated with fetal body and head growth, although it was associated with a higher risk of preterm birth. Evidence that SSRI drugs can pass through the placenta, with up to 72% of maternal levels detected in umbilical cord blood (Heikkinen, Ekblad, & Laine, 2002; Hendrick et al., 2003) further highlights the need for evidence-based psychological alternatives for the treatment of antenatal depression. No studies of maternal antenatal SSRI use were identified examining infant sleep, however animal research in this field suggests that exposure to SSRIs during the last week of gestation and during weaning led to alterations in the circadian system of the adult mouse with shorter free-running periods during constant darkness and larger light-induced phase advances (Kiryanova, Smith, Dyck, & Antle, 2012).

NICE guidelines recommend CBT or Interpersonal Psychotherapy (IPT) to treat depression during pregnancy, although the effectiveness and cost-effectiveness of these treatments during pregnancy have not yet been established (NICE, 2007). A literature search revealed a small number of studies assessing the efficacy of IPT for the treatment of depression during pregnancy; however, CBT has been largely overlooked with only a few published studies identified and only one study examining infant development following treatment of depression throughout the perinatal period (Rahman, Malik, Sikander, Roberts, & Creed, 2008).

A recent Cochrane Review by Dennis and colleagues (2007) identified only one study which met criteria to be included in the review of psychosocial and psychological interventions for treating antenatal depression (Spinelli, 2003). The authors repeated their search in March 2010 and identified an additional 12 new reports which are awaiting classification. The methodological quality of these studies was assessed using the Cochrane Reviews Handbook for Systematic Reviews of Interventions, which assesses studies on the basis of (i) selection bias (randomisation and allocation concealment), (ii) attrition bias (withdrawals, dropouts) and (iii) performance bias (blinding of participants, researchers and outcome assessment) (Higgins, Green, & Collaboration, 2008).

A study by McGregor examined 42 pregnant women allocated to CBT (n=21) or standard prenatal care (n=21) (McGregor, 2008). The CBT arm received six 5-10 minutes sessions of cognitive behavioural strategies, which were delivered by their obstetrical physician. Women were identified using a cut-off score of 9 on the EPDS. Depressive symptoms were again measured at 38 weeks gestation and 6 weeks postpartum. There were no differences between the two groups at 38 weeks gestation, although the groups were significantly different on their EPDS scores 6 weeks postpartum using a cut-off of 9 with the group receiving CBT showing a greater improvement. Taking into consideration the small number of participants and the low EPDS cut-off used to show significant differences between groups the findings should be interpreted cautiously.

A study by Grote and colleagues (2009) examined culturally relevant enhanced brief interpersonal psychotherapy (IPT-B) (n=25) versus enhanced usual care (n=28) in a group of low-income pregnant women. Depression was assessed using the EPDS and a cut-off of 12 was used to classify women as depressed. An intent-to-treat analysis indicated that women receiving IPT-B had lower levels of depression post-treatment and 6 months postpartum. Similar results emerged from a controlled trial comparing depression levels in pregnant women receiving IPT versus a parenting education programme (Spinelli & Endicott, 2003). Women meeting DSM-IV criteria were randomly assigned to the two groups and recovery was measured using three self-report measures (Beck Depression Inventory, EPDS and the Hamilton Depression Rating Scale). The IPT group scored significantly lower on all three measures compared to the education programme group. O'Mahen and colleagues (2013) examined the feasibility and symptom outcomes in a pilot RCT of modified CBT (mCBT) for women with low income. 55 women were randomly assigned to mCBT or treatment as usual (TAU). Women who received mCBT showed a greater improvement of depressive mood both at 16 weeks post-randomization and at the 3-month follow-up.

Online searches yielded 3 results for on-going or completed trials, which may be relevant to this study for which no published data was available⁴⁸(Brugha, 2010; Grote, 2010; Spinelli & Endicott, 2005).

⁴⁸ www.ukctg.nihr.ac.uk last accessed on March 6, 2013

www.clinicaltrials.gov last accessed on March 6, 2013

One study was identified which examined child outcome following treatment of depression in the antenatal and postnatal periods. Rahman and colleagues (2008) delivered an adapted CBT model to depressed pregnant women in rural Pakistan through health workers in a cluster randomised controlled trial. There were $n=463$ in the intervention group and $n=440$ in the control group. This was a large scale, well-designed and methodologically rigorous study. There were significant differences between the two groups at 6 and 12 months postpartum with fewer women with depression in the intervention arm. The authors, however, did not find differences in weight-for-age or height-for-age standardised scores in infants between those two groups, which were their primary outcomes. Significant differences were only evident in parenting practices and behaviours, which may nevertheless promote healthy infant development such as complete immunisation and increased play frequency with the infant for both mothers and fathers at 12 months postpartum.

A number of studies of other non-pharmacological therapies were identified in the literature search (Dennis & Allen, 2008) including:

- Light therapy (This was the only RCT - Epperson et al., 2004; Oren et al., 2002; Wirz-Justice et al., 2011)
- Music (Chang, Chen, & Huang, 2008),
- Acupuncture therapy (Manber, Schnyer, Allen, Rush, & Blasey, 2004; Manber et al., 2010; Ortiz et al., 2010)
- Massage (Field et al., 2009; Field et al., 2011; Field, Diego, Hernandez-Reif, Schanberg, & Kuhn, 2004; Field et al., 2008),
- Mindfulness (Beddoe, Paul Yang, Kennedy, Weiss, & Lee, 2009; Celedonia, 2009; Dunn, Hanieh, Roberts, & Powrie, 2012; Vieten & Astin, 2008),
- Antenatal education (Hayes, Muller, & Bradley, 2001)
- Psychotherapy (Freeman & Davis, 2010)
- Dietary supplements (Doornbos et al., 2009; Freeman et al., 2008; Lin & Su, 2007; Makrides et al., 2011; Rees, Austin, & Parker, 2008; Su et al., 2008).

Understanding and improving maternal depressive symptoms, which will benefit the mother but also potentially prevent some of the known adverse effects caused by

antenatal depression on child development, is of great importance. This study uses data from a pilot randomised controlled trial (RCT) of cognitive behavioural therapy (CBT) for depression during pregnancy to examine infant outcome 2 months postpartum.

5.1.1 Aims

Aim 1

To examine differences in infant sleep and temperament at 2 months of age in two groups of antenatally depressed women, one having received CBT and a second having received Care as Usual.

Hypothesis: It is hypothesized that women receiving CBT will have infants who:

- i) Score lower on the temperament scale/have easier temperament
- ii) Exhibit a longer sleep duration
- iii) Exhibit a lower number of awakenings at 2 months of age compared to those receiving treatment as usual.

Aim 2

To examine whether improvement in depressive symptoms with treatment is associated with infant sleep and temperament at 2 months of age.

Hypothesis: It is hypothesized that greater improvement of depressive symptoms during the antenatal period, will be associated with

- i) Lower scores on the infant temperament questionnaire
- ii) Longer sleep duration
- iii) Lower number of awakenings

5.2 METHODS

5.2.1 Design

This was a pilot randomised controlled trial (RCT) designed to assess the feasibility of CBT treatment of depression during pregnancy, focusing on the secondary outcomes of infant temperament and sleep.

5.2.2 Sample

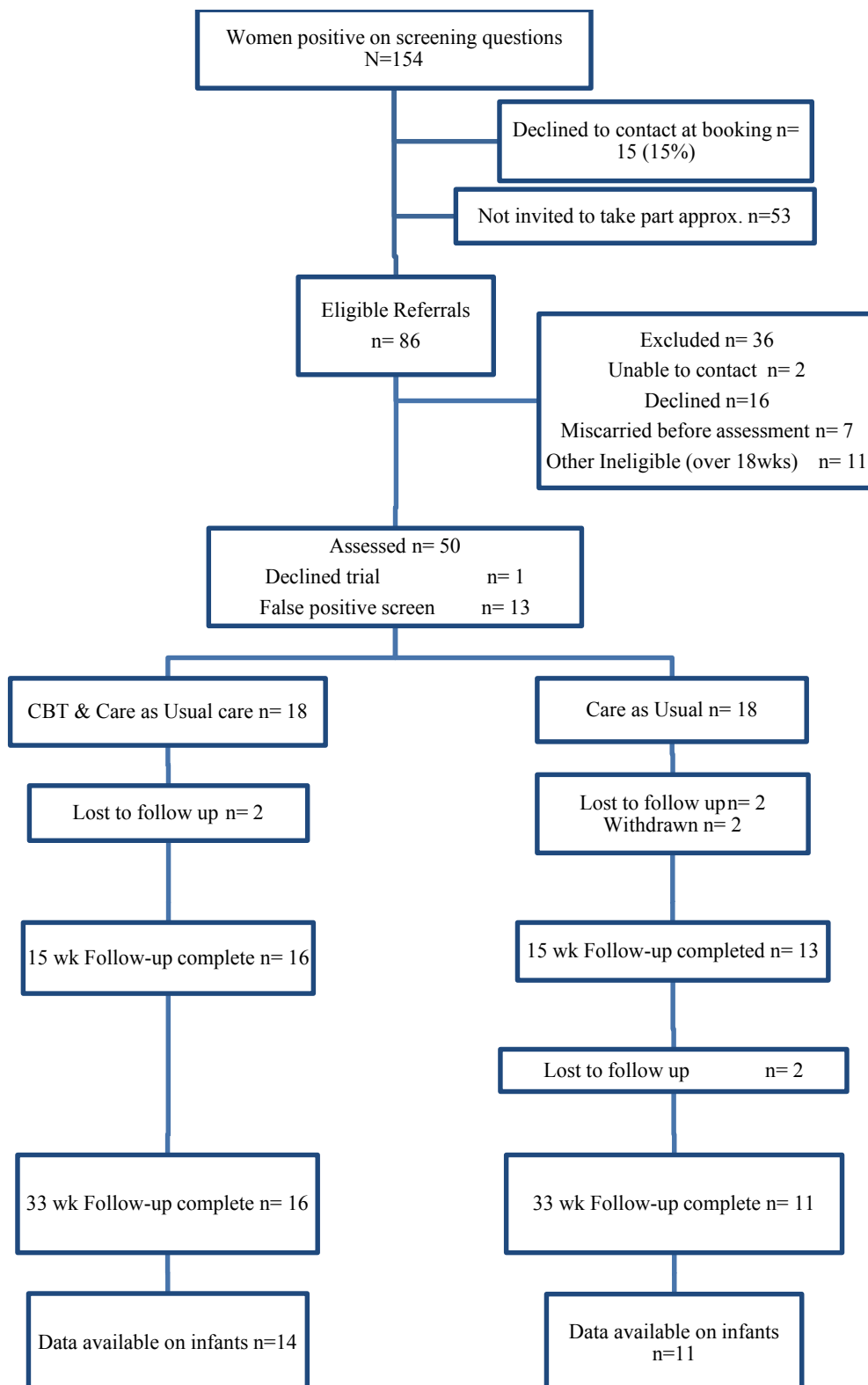
36 women were enrolled in the study and were randomised to Care as Usual or CBT plus Care as Usual. The flowchart describes attrition at each stage of the study (Figure 1). Demographic characteristics for the sample are presented in the table below by allocation arm. The analysis in this study includes participants who completed treatment ($n=36$) and for whom data on their infants' sleep and temperament were available (total $n=25$).

There were no differences between the two arms in terms of maternal age and number of weeks pregnant at baseline assessment ($t(34)=1.03$, $p=.310$, $t(34)=-.42$, $p=.677$) or baseline scores on the CIS-R and the EPDS ($t(34)=.72$, $p=.480$, $t(34)=1.01$, $p=.318$). No differences were found between groups for alcohol consumption or smoking (Fisher's exact test $p=.319$, $p=.637$) or for use of anti-depressants ($p=.143$). There were also no differences in infant gender between the two groups ($\chi^2(1)=.28$, $p=.701$), or breastfeeding rates (Fisher's exact test $p=.442$).

Table 49: Demographic characteristics presented by treatment arm (adapted from (Burns et al., 2013))

	N	CBT & Care as Usual	N	Care as Usual
Participant Characteristics				
Age: mean (SD, range)	18	28.2 yrs. (5.0: r= 20-36)	18	30.1 yrs. (6.2: r= 21-41)
No. of weeks pregnant at baseline assessment: mean (SD, range)		13 .1 wks. (3.2: r= 9-18)		12.7 wks. (2.2: r= 10-17)
Ethnicity White	13	72.2%	17	94.4%
No Religion	11	61.1%	12	66.7%
Married/ Cohabitation	13	72.2%	10	55.6%
Socio-economic indicators				
Working (full or part time)	12	66.7%	9	50%
Educational Qualification ('O' level or equivalent and above)	15	83.3%	16	88.9%
Financial Situation: Just getting by/difficult	12	66.7%	14	77.8%
Depression History				
Reported depression in the past	15	83.3%	16	88.9%
Current duration of depression (more than 3 months)	13	72.2%	13	72.2%
Use of antidepressants				
Never	12	75%	6	46.2%
Stopped when pregnant	2	12.5%	2	15.4%
Currently on antidepressants	2	12.5%	5	38.5%
Clinical variables				
ICD-10 Diagnosis				
Mild	3	16.7%	3	16.7%
Moderate	10	55.5%	10	55.5%
Severe	5	27.8%	5	27.8%
CIS-R Score: median (SD)	18	26.5 (7.9)	18	30.5 (7.5)
Antenatal depression EPDS: median	18	16.5 (4.3)	18	20 (5.1)
Reported been pregnant before	12	66.7%	12	66.7%
Ever smoked	10	55.5%	13	72.2%
Currently smoke	4	40%	5	38.5%
Currently consuming alcohol	3	20%	1	5.9%
Infant characteristics				
	n=15		n=11	
Infant gender:	15	7 female, 8 male	11	7 female, 4 male
Infant age (months)	10	1.93(.83)	14	2.20 (1.69)
Birth order (first born)	15	6/15	11	3/11
Prematurity	14	2 premature	16	0 premature
Birth weight	16	3422.7g (503.3g)	14	3180.21g (871.7g)
Breastfeeding (Yes)	14	(8/14) 57%	16	(12/16) 75%

Figure 18: Participant Flowchart adapted from (Burns, et al., 2013)



5.2.3 Measures

A flowchart of the measures collected at each time point is presented in Figure 19, page 238.

5.2.3.1 Depression

5.2.3.1.1 *Clinical Interview Schedule - Revised version (CIS-R)*

The CIS-R was administered to ascertain and ICD-10 diagnosis of mild, moderate or severe depression (Lewis, Pelosi, Araya, & Dunn, 1992). The CIS-R also gives a total score based on the duration and severity of depressive and neurotic symptoms. The measure was adapted for pregnancy related symptoms such as sleep, fatigue, and appetite, for which symptoms participants were asked to distinguish whether their experiences were related to their mood or pregnancy.

5.2.3.1.2 *Edinburgh Postnatal Depression Scale*

The Edinburgh Postnatal Depression Scale (EPDS) was computer administered to women at baseline (Time 1), at the end of treatment (15 weeks post randomization – Time 2) and 2 months postnatally (33 weeks post randomization – Time 3). This scale has been described in more detail in Chapter 2.

Change in depressive symptoms from baseline to post-treatment was calculated by subtracting the scores post-treatment from the baseline scores (Time 1-Time 2). A higher score on this variable indicates a greater improvement in depressive symptoms and a negative score an increase of depressive symptoms. A score of 0 indicates no change between baseline and post-treatment.

Where continuous scores of depression were used in the analysis, the EPDS was utilised, rather than continuous scores on the CIS-R for the following reasons.

- Firstly, due to the small sample size it was decided a priori to utilise one measure to avoid multiple testing.
- Secondly, the EPDS is the most widely used measure in the assessment of depressive symptoms in the perinatal period with a well-established cut-off score to indicate probable major depression.
- Finally, all other studies presented in this thesis have used the EPDS and this would allow for comparability across studies. A comparison of findings using the CIS-R scores is presented on p.242 for completeness.

5.2.3.2 Infant Temperament

The Infant Characteristics Questionnaire (ICQ) is a screening questionnaire developed to measure infant temperament using four sub-scales (Bates, Freeland, & Lounsbury, 1979), of which this study uses one: the *fussy-difficult* factor (see Appendix 45). This factor consists of nine questions and is a Likert-based scale with scores ranging from 1 to 7. Mothers completed the ICQ on average 2 months postpartum. A higher score on the questionnaire indicates a more difficult or demanding infant.

5.2.3.3 Infant Sleep

The Brief Infant Sleep Questionnaire (BISQ) was already described in section 4.2.4.2.4 page 188. An additional variable for sleep during the 24-hour period was calculated, by adding the nocturnal sleep duration and daytime sleep duration and subtracting the duration of wakefulness during night hours. *A priori* it was decided to focus on duration of sleep during the night and during the 24-hour period, and number of awakenings during the night, in line with most studies (including Chapters 2 & 3) and to limit the number of statistical tests.

5.2.4 Procedure

5.2.4.1 The trial

The pilot RCT (Trial Registration ISRCTN44902048) was conducted in North Bristol, UK, and was approved by the Southmead National Health Service Research Ethics Committee (09/H0102/75). The aim of this pilot trial was to assess the feasibility of a large RCT of individual cognitive behavioural therapy for depression during pregnancy. The primary outcome of the study was recovery according to the CIS-R. Secondary measures, examined here, included difficult temperament and sleep.

5.2.4.2 Recruitment

During their first appointment with midwives, women were approached about participating in the research. Women were eligible to participate if they were over 16 years of age and between weeks 8 and 18 of their pregnancy. They were eligible to take part if they had sufficient English to complete the questionnaires and to benefit from therapy without an interpreter.

Women were routinely asked by midwives about experiencing low mood or anhedonia and if they would like help with these symptoms (NICE, 2007). More specifically,

women were asked: ‘During the past month, have you been bothered by feeling down, depressed or hopeless?’ ‘During the past month, have you been bothered by having little interest or pleasure in doing things?’; ‘If yes is this something you feel you need or want help with?’ If they responded ‘yes’ subjects were invited to a pre-trial assessment. The 3-question screen was completed by the midwife and forwarded to the research team along with a permission to contact form. The research team then contacted the potential participant to arrange a baseline assessment.

The midwives did not invite 53 of the women that were identified by computerised NHS Bristol records as scoring positively on the screening items. The midwives reported the following reasons for not inviting these women: ‘misperceptions about the remit of CBT’, ‘woman too unwell for CBT’ or ‘CBT suited to those with phobias rather than depression’. Other reasons included: the midwives preferring to offer extra appointments with themselves, or assuming things were going well for the woman without actually asking the 3-question screen but completing the paperwork.

5.2.4.3 Baseline Assessment – Time 1

The baseline assessment, which was conducted in the mother’s home, included obtaining informed consent and completing the computerised version of the Clinical Interview Schedule-revised (CIS-R).

Women meeting ICD-10 criteria for depression (mild, moderate or severe) on the CIS-R were randomised to CBT plus Care as Usual or to continue with Care as Usual only. Allocation was determined through an internet-based randomisation service using a computer-generated code. Women were also asked whether they were already receiving CBT or another individual psychological therapy both of which were exclusion criteria. Participants were also excluded if they suffered from a psychotic illness or were receiving care from secondary mental health services.

There were four minimisation criteria: maternal age (< or >18), severity of depression (mild, moderate and severe as classified by CIS-R), duration of current symptoms of depression (< or > than 3 months) and a history of depression (yes, no). Participants were informed of the treatment arm to which they had been allocated at the end of the visit. The participant’s midwife and GP were also informed of their participation in the study. Women completed the baseline assessment at 13 weeks gestation on average.

5.2.4.4 Cognitive Behavioural Therapy (CBT)

The intervention was administered by two therapists and consisted of up to 12 weekly sessions of CBT in the home. An adequate dose of CBT was defined *a priori* as a minimum of 9 and maximum of 12 visits. 13 (out of 18) of the women receiving CBT completed 9 or more sessions (completion rate 72%). 10 of those women attended 12 sessions and 3 women attended 9. Two mental health professionals with post-qualification CBT training administered CBT.

5.2.4.5 Care as Usual

Both arms received Care as Usual from their midwives and GPs. This would involve 9 routine appointments with the midwife for primiparous women and 6 for multiparous women. They also have the option to book appointments at local health centres with family doctors. Referrals to specialist perinatal psychiatry services included phone counselling, psychological treatment or admission to a mother and baby unit.

5.2.4.6 Post Treatment Assessment – Time 2

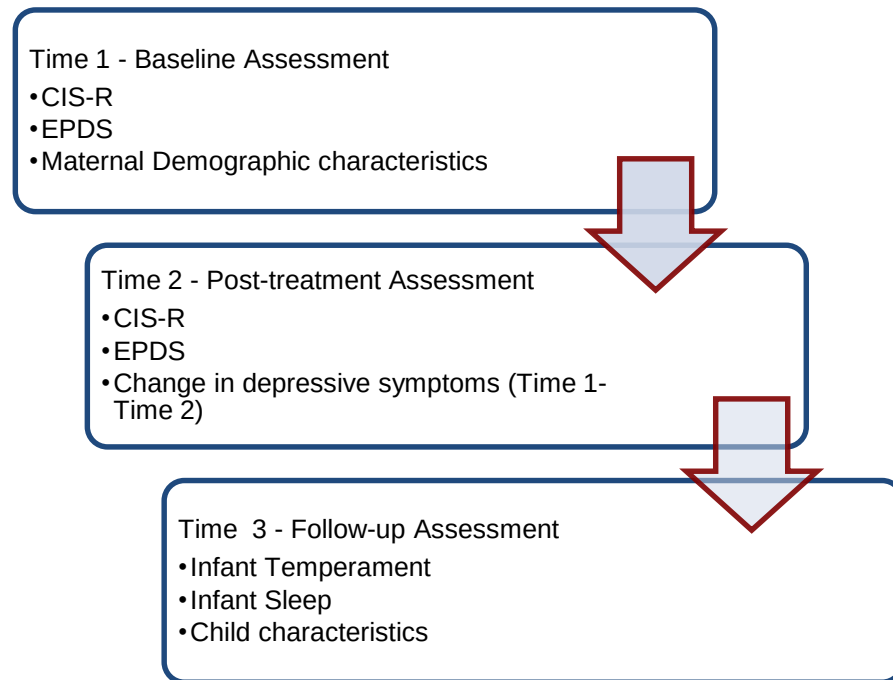
Women were assessed again post-intervention, which was up to 15 weeks after the baseline assessment. At this stage women were on average 32 weeks gestation. The visit included a repeat of the CIS-R and EPDS.

5.2.4.7 Postnatal Assessment – Time 3

The postnatal visit occurred 33 weeks after randomisation, when infants were 2 months old on average. The assessment included collection of data on infant temperament and sleep as well as the EPDS and CIS-R.

Replies were received from 101 women of whom 15 declined to participate. 86 women returned the consent-to-contact form; 36 were excluded either due to being over 18 weeks of gestation or miscarriage. An additional 13 women were excluded after pre-trial assessments, as they did not meet CIS-R criteria for diagnosis of depression. One woman did not want therapy and 36 were randomised, 18 to each arm. Figure 18 illustrates attrition of participants during the phases of the trial.

Figure 19: Flowchart of measures collected at each phase of the study.



5.2.5 Statistical Analysis

The outcome measures for this analysis were infant sleep and temperament, 2 months postpartum. The analysis was undertaken in the following steps:

1. Participant differences by treatment arm were examined.
2. A brief description of the analysis of the primary outcome of the study, treatment of depressive symptoms, which is presented in Burns and colleagues (2013), is provided here to provide context for the results that follow.
3. Descriptive statistics were examined for infant sleep and temperament as well as for depression scores using the EPDS and are presented by treatment arm.
4. Differences in infant temperament and sleep by treatment arm were examined (those receiving CBT vs. those receiving usual care only), using independent t-tests and Mann-Whitney U tests.
5. The associations between infant sleep, temperament and change in depression scores were examined, using bivariate associations (2-tailed Pearson or Spearman correlations according to normality of data) and were explored by treatment arm.
6. Associations between infant sleep, temperament and postnatal depression scores were examined using bivariate associations (2-tailed Pearson or Spearman correlations according to normality of data).
7. Where significant associations were found in step 5, a linear regression model was performed controlling for postnatal depression.
8. The association between change in depression scores and infant sleep was explored whilst controlling for temperament using linear regression.
9. Subsequent analysis was performed to explore the findings further. Two associations were explored in particular: first between baseline depression scores and change in depression scores from baseline to post-treatment; second, between infant sleep and parenting practices, specifically breastfeeding, which could confound the results.

5.3 RESULTS

5.3.1 Primary Outcome of RCT

Burns and colleagues (2013) have previously reported on the primary outcome of this study. The two groups differed significantly both at 15 and 33 weeks post randomisation when using continuous scores on the EPDS, with the group receiving CBT scoring significantly lower (Table 50). The table below presents the descriptives for depression scores using the EPDS at baseline, post treatment, postnatally and the change in depression between pre- and post-treatment. The data are also presented by treatment arm.

5.3.2 Descriptive Statistics

Table 51 presents descriptive statistics for sleep and temperament variables. Normality tests were performed on all variables⁴⁹. All variables were normally distributed with the exception of night awakenings (for statistical tests see footnote). Non-parametric tests were used for night awakenings.

5.3.3 Aim 1: Analysis by treatment arm

Differences between the group receiving CBT and the group receiving treatment as usual were examined and are presented in the table below. Independent t-tests and Mann-Whitney U tests were used. No differences were found for temperament or any of the sleep variables although a trend was found for sleep duration over the 24-hour period and for sleep duration over the day (Table 51). Children of mothers who received treatment as usual slept more than those who received CBT. Taking into account that the variable of sleep duration over the 24-hour period was constructed by adding sleep duration over the night and over the day it is not surprising that this trend is present in both variables.

⁴⁹ Temperament, S-W=.96, df=25, p=.366, Sleep duration over-night, S-W=.94, df=25, p=.170, Sleep duration over 24 hour period, S-W=.97, df=25, p=.624, Night awakenings S-W=.91, df=24, p=.039 (Kolmogorov-Smirnov tests were used).

Table 50: Descriptive statistics for depression scores.

	Care as Usual		CBT+ Care as Usual		Total		Test
	n	Mean(sd)	n	Mean (sd)	n	Mean(sd)	
EPDS Baseline Assessment	18	19.2 (5.2)	18	17.6(4.4)	36	18.36(4.77)	t(34)=1.01, p=.318
EPDS 15 weeks post-randomization	13	13.8 (7.5)	16	7.9 (4.7)	29	10.59(6.6)	t(27)=2.64, p=.014
EPDS 33 weeks post-randomization (in the postnatal period)	11	13.7 (6.2)	16	7.1 (4.8)	27	9.78(6.24)	t(25)=3.16, p=.004
EPDS Change from baseline to post-assessment	13	5.4(5.5)	16	9.8(5.4)	29	7.79 (5.78)	t(25)=-2.15, p=.041

Table 51: Descriptive Statistics for Infant Sleep and Temperament presented by treatment arm and test statistics to examine differences between the two groups.

	Care as Usual n=11		CBT + Care as Usual n=14		Total n=25		Test
	Mean	SD	Mean	SD	Mean	SD	
Difficult Temperament	32.36	6.65	31.64	9.84	31.96	8.43	t(23)=.208, p=.837
Sleep duration over-night	7.33	1.74	6.73	2.93	6.99	2.45	t(23)=.598, p=.556
Sleep duration over the day	7.09	3.7	4.7	2.63	5.75	3.3	t(23)=1.89, p=.071
Sleep duration over 24-hour period	14.42	3.39	11.43	4.19	12.74	4.08	t(23)=1.92, p=.067
Night time Awakenings	2.55	1.13	2.62	1.19	2.58	1.14	U(24)=73.5, p=.910

5.3.4 Aim 2: Associations between change in depressive symptoms, infant sleep and temperament

Associations between change in depression scores, temperament and sleep were examined using Pearson and Spearman two-tailed correlations and are presented in Table 52. A higher change in depression score was associated with a reduction in scores on the difficult temperament scale $r=-.45$, $p=.024$, and reduced sleep duration over the night $r=-.58$, $p=.003$. There was a positive trend between temperament and sleep duration overnight $r=.352$, $p=.084$. The results are also summarised in scatter plots below (Figures 20 and 21). The correlations were further explored in the CBT and Care as Usual groups separately. Due to the very small numbers results should be interpreted with caution, nevertheless, the correlations were significant in the CBT group (change in depression score with temperament $r=-.691$, $p=.006$ and with sleep duration $r=-.693$, $p=.006$). The correlations were not apparent however, in the Care as Usual group (change in depression score with temperament $r=-.07$, $p=.833$ and with sleep duration $r=-.39$, $p=.234$)⁵⁰.

⁵⁰ The analysis performed here was repeated using continuous scores on the CIS-R to examine whether results were comparable between the two depression measures. The analysis indicated that change in depression scores using the CIS-R (baseline CIS-R minus post-treatment CIS-R) was not associated with measures of temperament ($r=-.13$, $p=.532$), sleep duration during the night ($r=-.30$, $p=.139$), sleep during the 24-hour period ($r=-.09$, $p=.677$) or night awakenings ($r=.12$, $p=.579$) using two-tailed Pearson correlations. The CIS-R change scores showed a significant correlation with EPDS change scores ($r=.81$, $p<.001$). All associations were in the same direction with the exception of night awakenings and sleep duration during the day. The correlations and descriptives for CIS-R are presented in the Appendices, Appendix 43 & Appendix 44.

Table 52: Unadjusted associations between change in depression scores during pregnancy, infant temperament and sleep.

	EPDS Change	Difficult Temperament	Sleep duration over-night	Sleep duration over 24 hour period	Nighttime Awakenings	Sleep Duration over the Day
	r (p)	r (p)	r (p)	r (p)	r _s (p)	r (p)
EPDS change	_____	-.45*(.024)	- .58**(.003)	-.23(.264)	-.06(.791)	.142(.497)
Difficult Temperament		_____	.35(.084)	.29(.166)	.02(.910)	.091(.664)
Sleep duration over-night			_____	.59**(.002)	-.19(.383)	-.187(.383)
Sleep duration over 24 hour period				_____	-.18 (.397)	.799**(.000)
Night Awakenings					_____	-.207(.332)

*Correlation significant at the .05 level, ** Correlation significant at the .01 level

Figure 20: Scatter plots with regression lines a) of infant temperament with change in depression scores (n=25) and b) of infant temperament with change in depression scores by treatment arm CBT (n=14), Care as Usual (n=11).

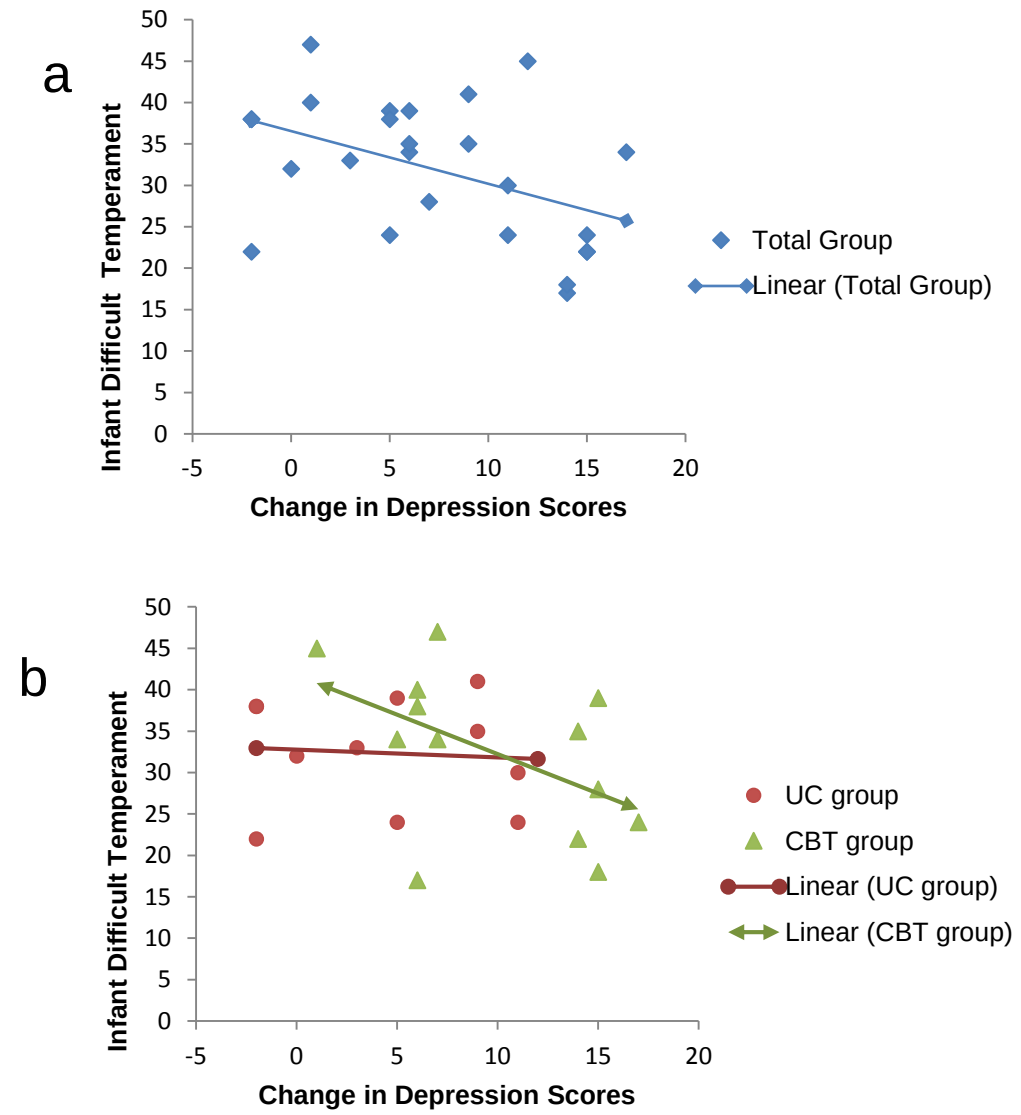
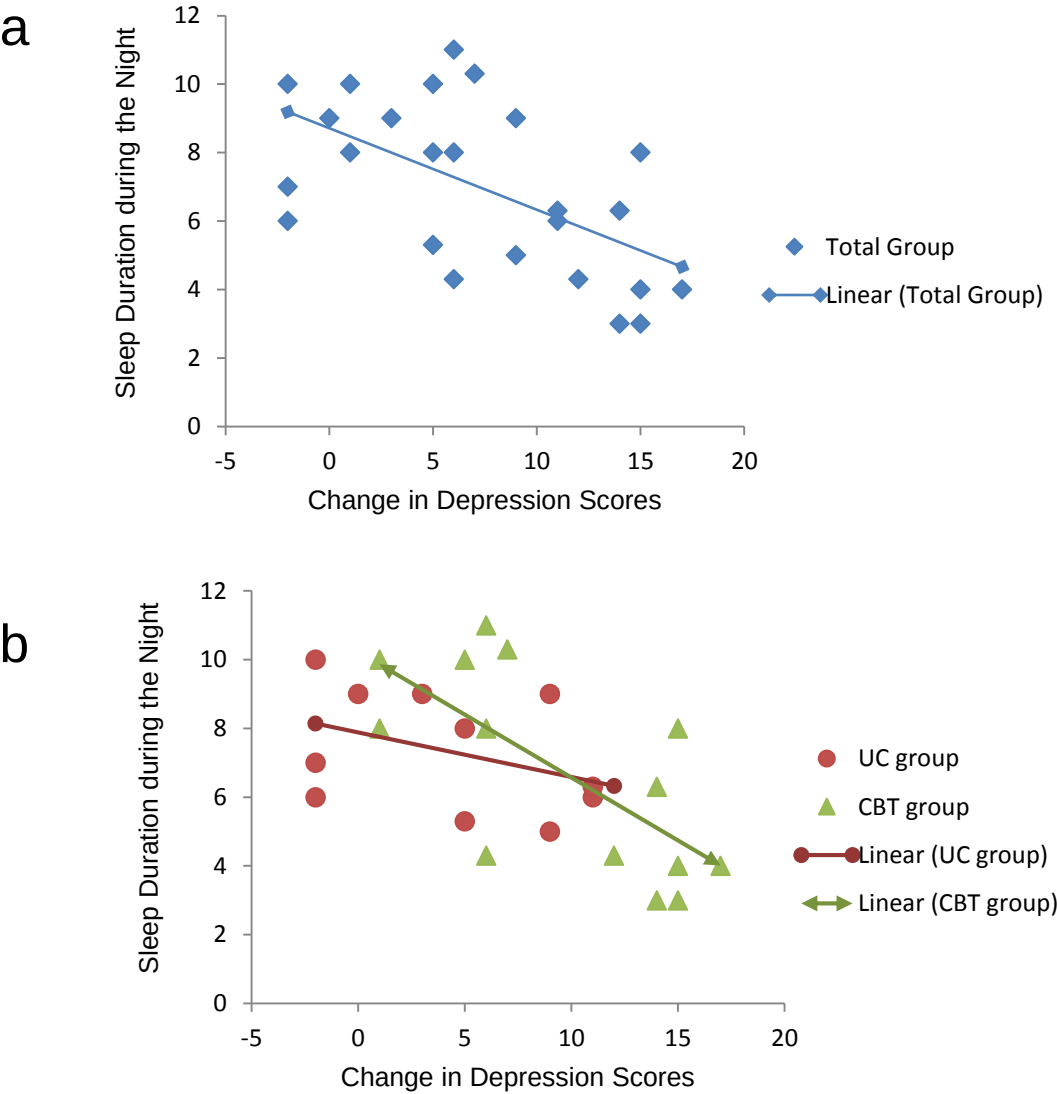


Figure 21: Scatter plots with regression lines a) of infant sleep duration during the night with change in depression scores (n=25) and b) of infant sleep duration during the night with change in depression scores by treatment arm CBT (n=14), Care as Usual (n=11).



5.3.5 Associations of Infant Sleep and Difficult Temperament with Postnatal depression

Bivariate associations were examined between postnatal depression scores and temperament and infant sleep (Table 53). Postnatal depression scores were associated with temperament, and sleep duration over-night.

Table 53: Unadjusted associations between postnatal depression, infant sleep and temperament.

	Postnatal Depression	Difficult Temperament	Sleep duration over 24 hour period	Sleep duration over- night	Night time Awakenings
Postnatal Depression	—	.42*(.036)	.19(.368)	.42*(.035)	.13(.559)

*Correlation is significant at the .05 level

5.3.5.1 Controlling for Postnatal Depression

Linear Regressions were examined to control for postnatal depression on the association between change in depression scores and 1) sleep and 2) temperament. Results indicated that, while controlling for postnatal depression, the association between temperament and change in depression scores did not hold (in Step 2 $\beta = -.30$, $p = .281$, in Step 1 $\beta = -.45$, $p = .024$). The association between sleep duration over-night and change in depression scores remained significant (in Step 2 $\beta = -.57$, $p = .035$, in Step 1 $\beta = -.57$, $p = .003$). In both models, postnatal depression did not predict temperament ($\beta = .200$, $p = .729$, $R^2 = .15$, $F(2,22) = 3.11$, $p = .065$) or sleep during the night ($\beta = .009$, $p = .972$, $R^2 = .33$, $F(2,22) = 5.50$, $p = .012$).

5.3.5.2 *Controlling for Infant Temperament*

There is extensive literature on the association between temperament and infant sleep (also discussed in Chapter 2) and this study reports a weak association between the two variables $r=.352$, $p=.084$. A linear regression model was therefore used to examine the association between change in depression scores and sleep during the night whilst controlling for temperament. Change in depression scores continued to predict sleep whilst controlling for temperament ($\beta=-.53$, $p=.013$). In Step 2 temperament did not predict sleep ($\beta=.116$, $p=.553$, $R^2=.34$, $F(2,22)=5.77$, $p=.010$).

5.3.6 Subsequent Analysis

5.3.6.1 *Associations between change in Depression Scores, Depression at Baseline and SSRI use*

Bivariate associations were examined between change in depression scores and baseline scores but the association was not found to be significant ($r=.217$, $p=.297$). There was also no difference in change in depression scores for women who had versus those who had not taken antidepressants (Table 54).

5.3.6.2 *Associations between maternal SSRI use and infant outcomes*

Independent samples t-test were used to examine whether SSRI use could account for any differences in infant sleep and temperament. No association was found between sleep duration during the night or temperament and maternal SSRI use (Table 54).

5.3.6.3 *Associations between breastfeeding and infant sleep*

The association between infant sleep and breastfeeding was explored to investigate whether this could account for the associations reported here, using independent samples t-test. No differences in temperament were found for women who breastfed and those who did not. No differences were found in infant sleep duration during the night. Similarly no differences were found in changes in depressive symptoms for women who breastfed versus those who did not.

Table 54: Differences in change in depression scores, temperament and sleep duration by i) maternal SSRI use and ii) by feeding mode.

	SSRI			no SSRI			Test Statistic
	Mean	SD	n	Mean	SD	n	
Change in depression scores	6.55	5.65	11	8.56	5.89	18	t(27)=.905, p=.373)
Temperament	33.67	7.26	9	31	9.1	16	t(23)=-.396, p=.696)
Sleep duration	7.25	1.72	9	6.84	2.82	16	t(23)=-.752, p=.459

	Breastfed			Did not breastfeed			Test Statistic
	Mean	SD	n	Mean	SD	n	
Change in depression scores	8.1	1.31	20	8.43	2.08	7	t(25)=0.129, p=.898
Temperament	33	7.39	17	32.12	8.90	7	t(22)=.231, p=.820
Sleep duration	6.9	2.76	17	7.03	2.46	7	t(22)=-0.113, p=.911

Summary of Findings

- i. There were no differences in infant sleep or difficult temperament according to treatment arm.
- ii. There were significant associations between change in depression scores from pre- to post- treatment and both infant difficult temperament and sleep duration over-night. Larger reductions in depressive symptoms during pregnancy were associated with easier temperament and shorter sleep duration.
- iii. Further analysis by treatment arm revealed this association to be significant in the CBT group, but not the Care as Usual group.
- iv. When controlling for postnatal depression, the association between change in depression scores and sleep duration remained. The association between change in depression scores and difficult temperament attenuated.

5.4 DISCUSSION

5.4.1 The findings

Aim 1

It was hypothesised that infants of women receiving CBT would exhibit an easier temperament, longer sleep duration and a lower number of awakenings. These hypotheses were not supported in this study. There were no significant differences between infants whose mothers received CBT and those whose mothers received Care as Usual in infant sleep or temperament. There was weak evidence, however, for differences in sleep duration during the day over the 24-hour period among infants whose mothers received CBT: such infants slept less compared to those whose mothers received Care as Usual.

Aim 2

The next step was to examine whether there were any associations between infant sleep, temperament and improvement in depression scores. Significant associations emerged for temperament and for nighttime sleep duration. A greater improvement in depression scores during pregnancy was associated with easier temperament and with shorter nighttime sleep duration. Further analysis of these findings by treatment arm indicated that these effects were stronger for those who had received CBT compared to those in the Care as Usual arm. Associations between infant sleep, temperament and postnatal depression were also examined. Both temperament and sleep duration during the night were significantly associated with postnatal depression. Linear regression models controlling for postnatal depression were examined to control for potential reporter bias. Associations between antenatal depression, infant sleep and temperament, whilst controlling for postnatal depression, indicated that the association between antenatal depression and sleep duration remained significant, whereas the association with temperament did not. The association between improvement in depression and sleep held whilst controlling for infant temperament.

5.4.2 Understanding the findings

As these are preliminary findings from a pilot study, they need to be interpreted cautiously before further replication has taken place. It should be noted that these may be chance findings; however, at this stage they are worth exploring as they may inform future research.

This study reported that improvement in depression scores was associated with temperament in accordance with the study hypothesis. This is also in line with a number of studies suggesting an association between antenatal depression and difficult temperament (Davis, et al., 2007a; McGrath, et al., 2008; Werner, et al., 2007). One explanation for these findings is programming effects, whereby antenatal depression predisposes the fetus to having more difficult temperament.

There was no evidence in the literature, however to suggest that improvement in depressive symptoms is associated with shorter sleep duration, as reported in this study. That this finding held whilst controlling for maternal postnatal depression would suggest that it was not a function of maternal reporting bias due to depressive symptomatology. An explanation specific to the findings of shorter sleep duration overnight suggests that these infants may be compensating with longer sleep time during the day. This potential explanation was taken into consideration. However, on further analysis no association was found between change in depressive symptoms and sleep duration during the day, suggesting that in this study infants were not compensating with longer sleep time during the day.

A number of participants reported a small number of hours of infant sleep during the night ($n=6$, <5 hours per night on average). This could have affected the results and is not in the expected range of hours spent sleeping during the night.

5.4.3 Potential Explanations

Taken together, the findings on temperament and sleep could be explained in the following ways.

First, mothers who have experienced improvement in their depressive symptoms may report infant behaviour more accurately. Similarly, mothers whose depressive symptoms have persisted or have worsened may be more biased towards reporting infant behaviour, particularly behaviour such as nighttime sleep duration which is not easily observed. A persistent low mood may affect ratings of infant temperament in a

negative way as mothers may feel dealing with a young infant harder. Particularly with reporting of sleep, pre-occupation with thoughts and feelings of low mood may affect the accuracy of reporting as mothers may not be as accurately aware of nighttime behaviour.

Improvement in depressive symptoms could lead to the perception that the baby has an easier temperament or is easier to manage. Many mothers suffering from perinatal depression report difficulties with caring for their infant, which could lead them to the perception that the infant is difficult.

An additional finding of this study was that the associations between change in depression scores and infant sleep and temperament were stronger in the group receiving CBT compared to those receiving usual care only. CBT might provide an additional benefit over and above the improvement of depressive symptoms alone. This may suggest that a set of skills or modifications in cognitive interpretations practised during CBT sessions help women engage with or perceive their children differently.

5.4.3.1 *Post Hoc Explanations*

A number of explanations were explored post hoc, which may account for, or have affected, the results. First, the use of antidepressant medication is an alternative and plausible biological mechanism which had not been accounted for in the statistical analysis. Evidence indicates that SSRIs cross the placenta in humans and that SSRI use has been associated with alterations to the circadian rhythm of the mouse (Hendrick, et al., 2003; Kiryanova, et al., 2012). No association was found in the change in depressive symptoms, infant sleep or temperament and SSRI use, suggesting that SSRI use is unlikely to have acted as a confounder in this sample.

A second additional factor explored post hoc relates to sleeping arrangement: 24 out of 25 infants slept in their parents' bedroom, which does not allow for any statistical tests due to the limited variability in data.

A third additional factor related to breastfeeding: it was hypothesized that breastfeeding could account for shorter sleep duration due to frequent nocturnal disruptions. There is evidence that breast milk is more easily digestible than formula milk, suggesting that some infants could require more feeding episodes to reach satiety. Post hoc analysis, however, did not indicate differences in sleep or temperament by feeding mode. Relevant to this point is also the general issue of feeding over-night. In this study

awakenings due to hunger were not separated from awakenings due to any other reasons. As feeding rhythms are independent of sleep-wake rhythms these may have affected the nocturnal total sleep duration.

Finally, post hoc associations between change in depression scores and baseline depression scores were not found to be significant. This suggests that participants with the highest scores at baseline were not more likely to show greater improvement post treatment. It may be hypothesized that there is greater scope for improvement of depressive symptoms among those scoring particularly highly, who would remain above the cut-off for probable clinical depression despite the improvement in depression scores.

The findings need to be interpreted cautiously as this was a small pilot RCT. Further replications with full-scale trials are needed in order to further understand what these findings may suggest. It is unclear whether the observed associations with infant temperament and sleep are consequences of the improvement of depressive symptoms or a combination of CBT and improved depressive symptoms.

There were a small number of extreme responders with regards to infant sleep, who reported fewer than 5 hours of infant sleep per night. These responders were all mothers who received CBT treatment. As this is not within the expected range of scores for sleep duration the findings should be interpreted cautiously. Looking at these cases specifically, three of them seemed to be compensating with sleep during the day (ranging from 6-10 hours) and three seemed to be having little sleep over the day (ranging from 1-3 hours). Future studies should examine the issue of compensating during the day as this may indicate different patterns in the entrainment of the light-dark cycle. Future studies should also consider including information on the time infants went to bed and woke up as there is no information in this study as to whether what is categorised as sleeping in the day was in fact continuous sleeping periods from late night to late morning.

One explanation is that improvement of depressive symptoms also impacts on the mechanisms through which antenatal depression impacts on child development and therefore, treatment has the potential to not only improve maternal well-being but also child development. As discussed earlier, one of the mechanisms through which antenatal depression is hypothesized to impact fetal development is through alterations

to the functioning of the HPA axis. In particular, an increased and sustained activation of the system would lead to higher levels of cortisol in the blood. A placental enzyme, known as 11 β -HSD2, regulates the transformation of cortisol into cortisone before it crosses the placenta. Levels of this enzyme in depressed pregnant women are reported to be lower and would lead to higher levels of cortisol crossing the placenta, thus affecting, fetal development. An improvement in depressive symptoms may decrease levels of cortisol in the blood which in turn would lead to lower levels of cortisol crossing the placenta, altering thus developmental trajectories.

Although a pilot, this is the first trial of CBT for depression during pregnancy, to deliver full CBT sessions administered by mental health care professionals. This was a pilot trial designed to examine whether this is a feasible way to recruit, assess and provide therapy for women during pregnancy. The design of this pilot trial presented an ideal opportunity to examine infant sleep and temperament, even though these were secondary outcomes. An experimental design such as an RCT can examine causal pathways, which association studies are not able to do. This is necessary both for understanding the exact mechanisms through which antenatal depression confers risk to child development and identifying effective methods and time points to intervene.

5.4.4 Strengths and Limitations

The study had a number of strengths, including the use of a clinical diagnosis for depression and reliable measures such as the EPDS and the ICQ temperament questionnaire. Women were randomised to each treatment arm and four minimisation criteria ensured that for these four known confounders the groups were similar (severity and duration of current episode of depression, history of depression and maternal age). Furthermore, CBT was administered by trained health care professionals who received adequate supervision from a clinical psychologist throughout the trial to ensure reliability. Data was collected at appropriate time intervals to address the aims of the study and the computerised assessment of depression guaranteed study blindness.

The study also suffered a number of limitations. Due to the small number of participants in each arm, controlling for a number of known confounders was not possible; however, minimisation criteria addressed some of these confounders. The analysis also did control for postnatal depression, a confounder relevant to both child development and

maternal reporting of child behaviour. A higher loss to follow-up was observed in the Care as Usual group compared to the CBT group. Although withdrawal from the study could not have been related to child characteristics such as difficult temperament, and therefore is unlikely to have specifically affected the results, it is an important note to make for future trials with this population group. Finally, the small sample size reduces the generalizability of the findings and highlights the need to interpret them cautiously.

This pilot trial was conducted to examine the feasibility of conducting a randomized controlled trial in this sample. For this reason, short questionnaires on infant temperament and sleep behaviour were utilised primarily to examine whether follow-up after birth would be feasible and to what extent mothers would complete the questionnaires. As these questionnaires heavily relied on maternal report, which may have been affected by maternal bias to the depressive symptoms, future studies should consider incorporating objective measures of infant sleep such as actigraphy or PSG. In particular, the areas of reporting which might have been affected the most are number of night time awakenings and sleep duration over-night, as the mother may not have been aware of her child waking up or of the duration of these awakenings, unless he/she sought parental attention.

Even in this small study it was possible to demonstrate that an improvement in depression symptoms can benefit child development as early as 2 months of age, suggesting that further research specifically looking at child development is needed.

In future, studies of antenatally depressed women and their infants should examine the effect of treatment of antenatal depression on biological measures such as cortisol reactivity in order to further delineate the mechanisms through which treatment can help both mothers and infants.

Chapter 6 Discussion

6 DISCUSSION

The overall aim of the thesis was to explore mechanisms through which antenatal depression may confer risk to the development of infant sleep. This was done using three overall approaches, which utilised different research designs: testing potential moderators and mediators and a direct response to treatment.

The objectives were:

- i. To examine the role of infant reactive temperament and the serotonin transporter promoter gene (5-HTTLPR) as potential moderators of the association between antenatal depression and infant sleep in two large population cohort studies; the ALSPAC and Generation R studies in the UK and The Netherlands respectively.
- ii. To examine the association between antenatal depression and infant sleep and explore potential mechanisms in a pilot study based in Oxford using detailed behavioural and physiological measures.
- iii. To examine sleep and temperament in infants whose mothers received CBT during pregnancy compared to a group of women who receive care as usual in a pilot RCT (ANTICIPATE trial).

The key findings of the thesis are:

- i. In accordance with the hypotheses set out in Chapter 2, infant reactivity acted as a moderator of the association between antenatal depression and infant sleep. Infants with reactive temperament and more specifically boys with reactive temperament are more susceptible to the effects of antenatal depression and exhibit shorter sleep duration, a higher number of awakenings and greater sleep problems. A moderating effect was found for nighttime awakenings at 18 and 30 months of age and for sleep problems at 18 months of age in the ALSPAC cohort. Reactive boys who had been exposed to antenatal depression exhibited a higher number of nighttime awakenings and sleep problems compared to all other groups. A similar finding emerged for the Dutch/European participants in the Generation R cohort for sleep duration at 24 months of age with reactive boys who had been exposed to antenatal depression displaying shorter sleep duration compared to all other groups.

Overall, 5-HTTLPR did not act as a moderator of the association between antenatal depression and infant sleep. The only exception to this was weak evidence of a moderating effect of 5-HTTLPR on the association between antenatal depression and awakenings at 24 month, which was limited to Generation R. Further exploration indicated that, contrary to our hypothesis, the finding was strongest for girls homozygous for the long allele (LL) who had been exposed to antenatal depression, who were reported to sleep longer.

- ii. In a pilot study using detailed observational measures, antenatal maternal depressive symptoms were found to be associated with maternal reports of infant shorter sleep duration but not with actigraphy derived sleep parameters. Postnatal depressive symptoms were consistently associated with shorter sleep duration in infants when using both subjective (maternal reports) and objective data (actigraphy). There was significant agreement between subjective and objective reports of infant sleep, which was in line with previous literature.
- iii. In a pilot randomized controlled trial, improvement in maternal depressive symptoms during pregnancy was associated with shorter sleep duration and easier temperament in infants at 2 months of age. The effect was strongest for the group receiving CBT, although there was no overall effect by treatment group.

The following sections explore the overarching themes of this research. Following this the overall strengths and limitations of this multi-method approach are considered. Finally, implications for research and public health are considered as well as directions for future research.

6.1 THE FINDINGS

Boys with reactive temperament are more susceptible to antenatal depression in relation to their sleep

This research provides preliminary evidence that infants are not susceptible to the effects of antenatal depression to the same degree; a finding that was reported in two European cohorts and at different time points in the early years of life. This finding is consistent with a growing body of evidence suggesting that some individuals are more susceptible to both positive and negative environmental influences (Belsky, et al.,

2007). Furthermore, this study is in line with a number of studies reporting temperamental reactivity as a marker of such susceptibility (Belsky & Pluess, 2009).

In both cohorts the evidence that infants are more susceptible to environmental influences was limited to boys. This is in line with a number of studies reporting boys with difficult/reactive temperament as more susceptible to environmental differences (Morgan, et al., 2012; Pitzer, et al., 2011). For example, van Aken and colleagues (2007) reported 16-19 months old infants with difficult temperament to show the smallest increase in externalizing problems when reared by highly sensitive mothers compared to insensitive mothers 6 months post assessment. Morrell and Murray (2003) reported that only highly distressed and irritable 4 month old boys who experienced coercive and rejecting mothering continued to exhibit emotional and behavioural dysregulation 5 months later. Lengua (2008) reported that anxious 8-12 year old boys who experienced inconsistent discipline were more likely to exhibit internalizing problems.

Further evidence that boys may be more susceptible has also been reported on the endophenotypic level, with boys with low vagal suppression being more anxious when growing up in high-conflict homes (El-Sheikh, Harger, & Whitson, 2001). On the genetic level in two reports boys low in MAOA activity were more likely to be diagnosed with conduct disorder following exposure to childhood adversity and more likely to experience mental health problems, particularly, ADHD if they were victims of abuse (Foley et al., 2004; Kim-Cohen et al., 2006).

Moving away from evidence specific to differential susceptibility and looking into potential sex differences in the programming effects of antenatal maternal mental health, Glover and Hill (2012) argue that, based on the animal literature on the effects of antenatal stress and offspring outcome, girls would be more likely to show an increase in emotional problems and boys in behavioural and learning. For example, male newborns of mothers with antenatal but not postnatal depression were reported to have lower scores on state regulation and motor skills (Gerardin et al., 2011). A number of studies have reported symptoms of ADHD to be associated with antenatal stress/depression specifically in boys (O'Connor, et al., 2003; Rodriguez & Bohlin, 2005).

Finally differences in fetal growth between boys and girls further suggests that looking at sex separately may reveal interesting patterns about early life development and its

determinants. For example, more boys show growth retardation and placental abnormalities, the rates of mortality in the first year of life are higher for boys than girls (5.4% vs. 4.1%) and in very preterm infants (23-24 weeks) the difference is even more pronounced (60% boys vs. 38% girls) (Di Renzo, Rosati, Sarti, Cruciani, & Cutuli, 2007; Ingemarsson, 2003). A recent study examining the mortality rates between males and females in the USA, using data from the Centre for Control Disease, during the years 1999-2008 reported males to have a higher mortality rate at all age groups from 0-20 years of age (Balsara, Faerber, Spinner, & Feudtner, 2013). When the rates were stratified by ICD-10 major disease categories (for example, congenital malformations, deformations and chromosomal abnormalities, diseases of the circulatory system of the nervous systems or the respiratory system or mental and behavioural disorders) they found males to have a higher mortality in 17 out of 19 categories.

Notably there was a finding specific to girls. As the findings were consistent across cohorts when the samples were ethnically homogeneous the role of ethnic and cultural background may likely moderate this association. Further studies and careful replication is required to understand the role of potential confounders and moderators of this association.

Several factors have been hypothesised to contribute across the lifespan to these higher mortality rates including health reporting behaviours, healthcare utilization and biology. Particularly with biology, two hypotheses could contribute to these findings first, hormonal changes stemming from male-specific genes and second, the chromosomal make-up of XX for females and XY for males.

No evidence of a moderating effect by 5-HTTLPR

This is the first study to our knowledge, to examine the moderating effect of 5-HTTLPR on the association between antenatal depression and infant sleep. This study did not find evidence to suggest that 5-HTTLPR moderates this association. This is in line with recent work by Braithwaite and colleagues (2013) where we reported no moderating effect of 5-HTTLPR in the ALSPAC cohort for the association between antenatal anxiety and child emotional and behavioural problems at 6 months, 4 and 13 years of age. A number of studies have reported positive findings for a moderating effect of 5-HTTLPR on the association between early adversity and later development, with carriers of the 's' allele as more susceptible to the effects of the environment. This was

also reported in the study by Pluess and colleagues (2010) in the Generation R cohort, who reported that carriers of the 's' allele who had been exposed to antenatal depression had more difficult temperament at 6 months of age. However, as was discussed in detail in Chapter 3 the findings in this field are equivocal. To date, two meta-analyses report negative results, a recent meta-analysis by Karg et al. (2011) has been criticized for lenient inclusion criteria in the meta-analysis and reports on the statistical power of GxE studies point towards potential false-positive results (Duncan, 2013; Duncan & Keller, 2011; Fergusson, Horwood, Miller, & Kennedy, 2011; Karg, et al., 2011; Munafò, Durrant, Lewis, & Flint, 2009; Risch, et al., 2009).

A single moderating effect is reported here for the Generation R cohort for awakenings at 24 months however; the findings were in the opposite of the expected direction with girls homozygous to the 'l' allele more susceptible to the effects of antenatal depression. As has been discussed in more detail in Chapter 3, the discrepancy between these and published findings could be due to a number of reasons.

- i. Sleep is known to be a complex behavioural state and is likely to arise as the result of an interaction between multiple genes and environmental factors.
- ii. Earlier investigations in this field, which reported positive results of a moderating effect, were conducted in smaller sample sizes, which may represent a Type I error (false positive). Furthermore, failure to achieve Hardy-Weinberg equilibrium in the distribution of alleles may have skewed the data and the results. According to Duncan 96% of novel reports of GxE interactions reported positive results versus only 27% of replication studies (Duncan, 2013). More recent studies such as the one by Braithwaite and colleagues (2013) with larger sample sizes suggest that the association between early life adversity and 5-HTTLPR may be more subtle and complex than previously thought.
- iii. Earlier investigations of a moderating effect of 5-HTTLPR were examined using maltreatment, abuse or stressful life events experienced early on in life and their association to later development (Caspi, et al., 2003). In this study antenatal depression was examined as a marker of adversity experienced during fetal life. The effect of antenatal depression however may not be as strong as that of abuse or stressful life events or may have significantly different mechanisms, and may thus not interact with 5-HTTLPR in the same way to predict later development.

Investigating infant sleep using objective measures

Chapter 4 reported an association between antenatal depression and maternal reports of infant sleep duration. This is in line with previous research (Armitage, et al., 2009; Armstrong, et al., 1998; Nevarez, et al., 2010). It is interesting to note that this association was not found in the actigraphy data. Replication of these results is required before making any firm conclusions, however, this study does suggest that a multitude of factors, even during the early stages of life, contribute to infant sleep and that monitoring maternal mental health from the antenatal period is important for both mothers and babies. The findings are also in accordance with animal research in this field. Further understanding of the association between antenatal mood disturbance and infant sleep may contribute to our understanding of the impact of sleep quality on a number of developmental and health outcomes later in life.

This study discussed significant recruitment and feasibility issues encountered during this study. These are taken into consideration and have already informed future research with this group. The low uptake for the study might have been partly due to the objective measures used, which are time consuming for both participants and researchers. Continuous direct monitoring remains the more accurate way for data collection. In future, technology advances and unobtrusive monitoring with devices, which will have the capability to transmit directly to electronic receivers, will make data collection easier.

Improvement in maternal mood is associated with infant sleep and temperament

Chapter 5 reported that improvement in maternal depression in the context of a treatment trial was associated with easier infant temperament and shorter sleep duration. This, to our knowledge was the first RCT for women with antenatal depression, which also examined child developmental outcomes. Only one other RCT in the perinatal period was identified in the literature, which did not find any differences in weight-for-age and height-for-age standardized scores in infants of mothers who received treatment throughout the perinatal period versus those who did not (Rahman, et al., 2008). This is the first study to report an association between improvement in maternal antenatal depressive symptoms and child outcomes in the early postnatal period. The finding of a stronger effect for the group receiving CBT treatment suggests that addressing maternal mental health during pregnancy may have beneficial effects for child development. The exact mechanisms remain unclear however, it is possible that improvement in maternal

depressive symptoms may lead to a mother's increased sense of confidence in dealing with a young baby and to improved mother-infant interaction.

In animal research, where experimental manipulation of rearing environments is possible, it has been shown that the effects of antenatal stress may span across generations of offspring and are reversible with timely interventions (Ward et al., 2013; Weaver, et al., 2004). Examining the effects of psychological treatments for antenatal mood disturbances are important first, due to the low acceptability of pharmacological treatments and their potential effects on fetal development and second, due to the potential of psychological treatments to not only improve mood but also positively impact on parenting skills therefore, affecting the postnatal rearing environment.

6.2 THE CONCEPT OF OPTIMAL SLEEP

Throughout this thesis the construct of sleep has been discussed. It is worth noting that the populations studied in this research were not presenting with clinical levels of sleep disturbances and analysis was not conducted in such a way as to identify those with potential clinical levels of sleep disturbances. In the variable of sleep no optimal levels of sleep were identified or used for this analysis (eg optimal sleep duration or number of awakenings). Particularly with sleep early on, what constitutes optimal sleep will depend on what is optimal for infant development and what is optimal for the infant's caregiver who is often completing the information on infant sleep. Unlike the case of emotional and behavioural problems for example, a widely used outcome in this area, where a higher number of symptoms indicates a higher presence or severity of emotional and behavioural problems, in the case of sleep longer sleep duration or no awakenings cannot invariably be interpreted as the optimal outcome. This is an important issue when attempting to interpret the findings and considering the implications of this research.

6.3 DIFFERENT METHODOLOGICAL APPROACHES

When considering the complexity of the association of antenatal depression with infant sleep it is evident that a variety of methodologies are required as well as research of an interdisciplinary nature to further our understanding on this topic. The different methodological designs used in this thesis are described below.

Large cohort studies

This thesis utilized two large longitudinal cohort studies, which allowed for the study of infant sleep over a prolonged period and with multiple assessment time points. The prospective design of these studies allowed for more accurate data collection as it was collected at the actual time rather than retrospectively. This is important particularly with respect to maternal depression where recall bias might have affected results.

Longitudinal cohorts are also particularly useful in clarifying the temporal order of risk and outcome such as the ones examined here of antenatal depression and infant sleep.

An additional advantage of using these studies was their sample size, which allowed for testing moderation models, using interaction terms, whilst controlling for a number of confounding variables, which is not always possible with small sample sizes. Additionally a large sample size is necessary when considering the possible contribution of genetic factors such as the one addressed here, in order to achieve the necessary statistical power. Finally large population-based sample sizes provide some confidence that findings are more generalizable.

The financial and time cost of conducting studies of this scale cannot be underestimated. For this thesis data had already been collected by the time this thesis commenced and thus, these disadvantages did not directly affect this research, however, large amounts of resources are necessary to achieve cohorts of this size. As a direct result, careful consideration is given to the measures to be included. In depth objective measurement will not always be possible for all variables due to the cost incurred by the study and time investment on the side of the participant. Similarly, as is the case in ALSPAC and Generation R, with particularly costly measures such as collection of data on 5-HTTLPR alleles, often sub-samples of the cohort will be included. As data collection for both cohorts had already been completed prior this thesis, it was not possible to determine the most appropriate aspects of sleep behaviour to be examined or the time points. As a result there is a discrepancy between the two cohorts, namely only one time point of assessment (at 6 months) coincides for ALSPAC and Generation R, and a variable of potential clinical importance relating to infant sleep available in ALSPAC – sleep problems- was not available in Generation R.

A significant disadvantage of large cohorts, which span over a number of years, is selective attrition. In this thesis, the included and lost-to-follow-up samples differed in

terms of educational qualification and depression scores with included samples, having attained higher educational qualification and scoring lower on depression.

Cross- Cohort Analysis

In two chapters in this thesis potential moderators of the association between antenatal depression and infant sleep were examined in two cohorts allowing for the results to be compared in two distinct population groups (Batenburg-Eddes et al., 2012; Copeland et al., 2013). This analysis adds to a small number of identified studies, which have used multiple longitudinal epidemiologic cohorts to address the same question allowing for a discussion of cross-cohort consistency of findings. A key issue with findings particularly in the GxE field (as already discussed in Chapter 3) is the issue of chance findings and publication bias. Publication bias refers to the publishing (or not publishing) of findings based on the nature and direction of the results. Statistically significant and positive results are more likely to be published, and to be published rapidly. They are also more likely to be published more than once and more likely to be cited by others (Higgins, et al., 2008). Examining findings across multiple cohorts can act as a good defence against chance findings.

Detailed Observational Studies

The study also utilized a pilot observational study. The advantages of such small studies include the opportunity of conducting in-depth assessments that may require more time invested on both the researcher and participant side. For example, this study utilized objective data on maternal and infant sleep and employed a diagnostic interview to identify depressive symptoms. This is a significant advantage of small-scale studies as in depth investigations involving long term recordings of sleep are rarely feasible in large-scale studies. In this study, continuous direct monitoring of rest/activity patterns for two weeks antenatally and two weeks postnatally was employed. Furthermore, as was discussed in Chapter 4, mothers were informed that the aim of the study was infant sleep and were asked to report daily on infant sleep behaviours for two weeks. This may have allowed for better quality data as the mother was focusing on one aspect of child behaviour compared to for example, the cohorts described above, where questionnaires would have assessed many aspects of child development. This approach is not without limitation of course, and may have contributed to recruitment difficulties, as women

may have been reluctant to commit to the requirement of a two week sleep recording and diary keeping. The small sample size limits the generalizability of the findings.

Randomised controlled trials

This research and previous literature indicate that there is a statistical association between antenatal depression and infant sleep. However in order to establish whether this may be an association of cause and effect requires further consideration. Bradford Hill identified nine criteria which can aid in the judgment of whether an association is causal or not, including the strength of the association, the consistency and specificity of findings, the temporal sequence and evidence of a dose-response relationship, the biological credibility of the hypothesis, the coherence of findings and experimental evidence (Hill, 1965).

The two designs discussed above only provide a certain degree of evidence (most notably the strength, consistency and temporality of the association) for assessing whether antenatal depression has a causal role in the development of infant sleep disturbances. However the strongest evidence for a causal association is that provided by experiment. The final study design, a randomized controlled trial (RCT), was utilized to examine whether treatment of antenatal depression was associated with child outcome in an experimental paradigm. RCTs are considered the gold standard to establish causation as they “provide a much needed control that allows rigorous testing of the causal hypothesis and takes account of unmeasured confounders” (p.377 Rutter, 2007).

There are several strengths to employing an RCT. Firstly, participants are randomly allocated to each treatment arm and provided the study is of sufficient size, the two groups are thereby matched on a number of pre-defined characteristics, which have the potential to confound the study. In addition it is also possible to use minimization criteria, whereby specific characteristics, that are deemed to be particularly important, are matched for within the randomization process. For example in the study in Chapter 5, the minimization criteria included age, severity and history of depression.

Furthermore, baseline and post-treatment data collection can be conducted by researchers who are blind to the participants’ treatment allocation to ensure this does not influence the recording of outcomes or the data analysis.

6.4 OVERALL STRENGTHS AND LIMITATIONS OF THE THESIS

The individual studies reported in this thesis have specific strengths and limitations, which have been discussed in chapters 2-5. This section will address the overall strengths and limitations of this multi-method approach to addressing the aims of the thesis.

6.4.1 Strengths

This thesis addresses several aims and provides us with novel findings in the field of antenatal depression and infant sleep. The studies reported here were the first to address the moderating role of infant reactivity and 5-HTTLPR in relation to infant sleep, using a two-cohort study design. It is also the first to examine prospectively the association between antenatal depression and infant sleep using objective behavioural and physiological measures and the first to examine child outcomes in the context of an RCT, which treated women with antenatal depression during pregnancy.

This thesis used prospective study designs throughout to assess both antenatal depression and infant sleep thus, avoiding issues of retrospective reporting bias, and addressing Bradford Hill's "temporal" criteria.

An important advantage of this multi-design approach is that it has allowed the examination of different aspects of the same research question, compared to having undertaken only one study which may have only given one particular form of information. These different approaches inform each other, and give the opportunity to appreciate a rounded and more complete picture of the association investigated here. Having used two cohorts to examine some of the aims of this thesis, gives confidence that the findings presented here are less likely to be chance findings.

Finally, this multi-method approach has given me the opportunity to receive training in several different methodologies and disciplinary approaches.

6.4.2 Limitations

A significant limitation of the thesis relates to selective attrition bias often seen in longitudinal studies such as the ALSPAC and Generation R. In these two cohorts attrition and loss of data to follow-up at the point of analysis amounted to approximately 36.1% for ALSPAC and 69.3% for Generation R. This limitation of missing data may

have affected the results as this was selective and not random attrition, as can be seen in Methods sections (Chapters 2 & 3). The analysis of included versus total samples (section 2.2.1.2) revealed that the included samples had higher educational qualifications and scored lower on maternal depression levels. Imputation models were considered, but were not used, as the majority of data lost was due to incomplete questionnaire data for antenatal depression (the predictor) and infant sleep (outcome).

The generalizability of the findings may be limited due to the ethnic composition of the study samples examined here. The ALSPAC cohort is a homogeneous study consisting of almost 98% participants of White background and the Generation R of 75% Dutch/European participants. Where the analysis involved the group of culturally diverse participants the results indicated the ethnic background did act as a confounder, this is consistent with other investigations of infant sleep (Galland, et al., 2012). The Oxford Sleep Study and Anticipate trial both had small sample sizes and without further replications no firm conclusions can be made as to the generalizability of these findings. In both studies, the samples were again predominantly of White background.

Another limitation of this thesis is the reliance on maternal report for both dependent and independent variables. An exception to this was the inclusion of actigraphy for the measurement of infant sleep in Chapter 4, which showed a high correlation to maternal report at two months of age. In large cohorts such as the ALSPAC and Generation R, objective measures are not always possible due to the scale of the study and the financial and time costing implications these may have. Inclusion of paternal reports to corroborate data collected from mothers was attempted in the smaller detailed study, however paternal participation was very low.

In the studies discussed here it was not possible to examine fetal development and to establish therefore a direct link between antenatal depression and potential rest/activity patterns in the fetus or other changes in the intra-uterine environment that have the potential to impact on infant sleep. This option was explored for the study described in Chapter 4. One established device was identified in the Department of Sleep Disorders Research, Tokyo Metropolitan Institute of Medical Science. Following communication with the founders of this device, it was decided that this would not be a viable solution as at the time of study planning the device software for data collection and analysis was only available in Japanese (Ryo, Nishihara, Matsumoto, & Kamata, 2012).

Finally, a disadvantage of having employed a multi-method approach is that less time can be spent on any single study. This may have affected results in Chapter 4; had it been the sole focus of this thesis, the numbers recruited may have been higher.

6.5 IMPLICATIONS

6.5.1 For Future Research

The findings of this thesis have four important implications for research.

This thesis highlights that not all infants are susceptible to environmental influences to the same degree and this is the first study to indicate this in relation to infant sleep development. Second, sleep is a complex, currently unexplored and promising area of child development in relation to the effects of the antenatal environment. The thesis underscores the advantages of combining psychological and physiological measures in assessing infant sleep and development. Third, this thesis has identified some of the practical constraints of conducting detailed observational research with women in the third trimester of pregnancy particularly those who may be suffering from low mood, as well as some of the difficulties of collecting physiological measures from young infants, which will hopefully inform future research. Finally, this thesis highlighted the need for cross-cultural research in further understanding the association between antenatal depression and infant sleep.

6.5.2 For Public Health

This thesis has identified the following implications for public health policy.

First when targeting interventions this study has identified that infants are not equally susceptible to the effects of antenatal depression. This finding was replicated in two cohorts and identified that boys with high reactivity may be more susceptible. More detailed intervention studies with high-risk groups may provide further causal evidence as to whether boys with high reactivity are indeed more susceptible to the effects of antenatal depression. This further step is needed before targeted interventions should be considered. This finding was limited to the area of infant sleep but may extend to other areas of child development. The finding of girls in the high reactivity group who were more susceptible to longer sleep duration if their mother had reported depressive symptoms during pregnancy, which was limited to the Generation R cohort was in

opposite direction and further highlights the need to examine gender differences separately and potentially tailor interventions accordingly.

Furthermore, this thesis has discussed preliminary evidence from a pilot RCT to suggest that treatment of depression during pregnancy may have beneficial effects for both the mother and the infant. Again, this requires confirmation in a full-scale RCT to examine these effects in more detail. However it does provide suggestive evidence that the benefits of treatment for antenatal maternal depression may extend beyond the mother to their developing fetus. Whether these be indirectly through improved mother-infant interaction or through physiological mechanisms remains to be determined.

6.5.3 Further Investigation

There are a number of key ways in which investigations in this relatively unexplored area may contribute to our understanding of both the effect of maternal antenatal health on child development as well as the origins of sleep disturbances.

First, this research did not investigate the association between antenatal depression and fetal rest/activity patterns or sleep, an association, which would have suggested a direct mechanism through which antenatal depression impacts on infant sleep. Establishing this continuum between fetal and infant states is crucial in ascertaining that this association is not the result of unobserved or unmeasured variables. Although this option was explored for the Oxford Sleep Study it was not feasible and was not available for ALSPAC or ANTICIPATE. In order to further disentangle the effects of the intrauterine environment some natural experiments may also be ideally designed to further disentangle the contribution of antenatal mental health on infant sleep. One example is adoption studies; in particular adoption at conception studies. These present as an ideal means of naturally separating the antenatal from the postnatal environment (Rice et al., 2009; Rutter, 2007). Alternative natural experiments would include pregnant women who have experienced natural disasters such as earthquakes, hurricanes or ice storms which could lead to short-term acute stress or long-term stress due to the consequences of the disaster (Kinney, Miller, Crowley, Huang, & Gerber, 2008; Laplante, Brunet, Schmitz, Ciampi, & King, 2008). This design could be particularly helpful in disentangling the effects on child development during different

developmental periods, as participants would have been affected during different trimesters.

Second, this and other studies, have already suggested ethnicity as an important moderator of sleep. It is important to explore the potential effects that different cultural practices may have in influencing patterns of infant sleep and the developmental trajectories over the first few years of life.

Third, paternal contribution has been largely overlooked in the study of child development, with the majority of studies utilising maternal reports of child behaviour. One of the studies in the thesis attempted to examine paternal contribution, however low participation from fathers prevented analysis of data. This is an important feasibility issue to consider. Including fathers can be of great benefit for the following reasons. Paternal reports could provide data from a second rater for child behaviour and sleep. Particularly for investigations of maternal depression and infant sleep, paternal reports may help control for potential reporter bias. Secondly, including fathers can help delineate the contribution of the intra-uterine environment to disturbed infant sleep. The underlying assumption in the field is that maternal depression influences the intra-uterine environment, which in turn has a direct biological effect on fetal/infant sleep. By including fathers it is possible to establish the genetic contribution of mother and father, which should be of equal load. However, if the intra-uterine environment contributed to the risk of disturbed sleep then contribution from maternal antenatal depression should be higher than that of paternal antenatal depression.

Finally, it is important to establish whether the findings reported in this research hold at later time points when sleep patterns have become more established.

6.5.4 Conclusion

In conclusion, this thesis has presented evidence that antenatal depression is associated with infant sleep when using maternal reports. Objective measures of infant sleep, although an important and feasible avenue to explore, were not associated with infant sleep in this study. Not all infants are equally susceptible to environmental influences and this may prove important in targeting interventions. However, the role of genetic factors in conferring any susceptibility remains unclear. Finally, psychological

interventions during pregnancy do appear to have beneficial effects for mothers and potentially indirectly to child development.

LIST OF APPENDICES

Appendix 1: Comparison of IBQ-R as used by Generation R (Pluess 2011 - negative emotionality) and Carey as used by ALSPAC (Ramchandani 2010 -reactivity).....	276
Appendix 2: Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and number night awakenings at 6 months, n=8,909 ...	281
Appendix 3: Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and total sleep time at 18 months, n=8,318	282
Appendix 4: Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and number of awakenings at 18 months, n=8,310	283
Appendix 5: Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and total sleep problems at 18 months, n=8,423	284
Appendix 6: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and total sleep time at 30 months of age, n=7,816	285
Appendix 7 Hierarchical Regression Analysis testing the moderating effect reactivity on antenatal depression and number of awakenings at 30 months, n=7,877	286
Appendix 8: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and total sleep problems at 30 months n=7,692	287
Appendix 9: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and total sleep duration at 6 months n=2,241.....	288
Appendix 10: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and number of night awakenings at 6 months n=2,169	289
Appendix 11: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and total sleep duration at 24 months n=1,898.....	290
Appendix 12: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and number of night awakenings at 24months n=1,974.....	291
Appendix 13: Unadjusted association for sleep items for participants with genetic data.....	293
Appendix 14: Unadjusted associations between sleep variables, antenatal depression, 5-HTTLPR and covariates at 6 months (n=4229).....	294
Appendix 15: Unadjusted associations between variables at 18 month (n=4,179)	295
Appendix 16: Unadjusted associations between variables at 30 months (n=4,025).....	296
Appendix 17: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 6 months, n=4,119.	297

Appendix 18: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and number nighttime awakenings at 6 months, n=4,229.....	298
Appendix 19: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 18 months, n=4,131.	299
Appendix 20: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and number nighttime awakenings at 18 months, n=4,133.....	300
Appendix 21: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep problems at 18 months, n=4,179.....	301
Appendix 22: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 30 months, n=4,131	302
Appendix 23: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and number nighttime awakenings at 30 months, n=4,133.....	303
Appendix 24: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep problems at 30 months, n=4,179.....	304
Appendix 25: Unadjusted associations between sleep variables, antenatal depression and covariates.	305
Appendix 26: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 6 months in Generation R, n=1,317.....	306
Appendix 27: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and awakenings at 6 months in Generation R, n=1,283	307
Appendix 28: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 24 months in Generation R, n=1,626.....	308
Appendix 29: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 24 months in Generation R, n=1,677.....	309
Appendix 30: The Edinburgh Postnatal Depression Scale (EPDS).....	311
Appendix 31: Questionnaire on demographics characteristics of participants	312
Appendix 32: Pittsburgh Sleep Quality Index	315
Appendix 33: The State Trait Anxiety inventory	317
Appendix 34: Stressful Life Events Questionnaire	318
Appendix 35: The Brief Sleep Quality Index	319
Appendix 36: Maternal cognitions about infant sleep questionnaire	320

Appendix 37: Actigraphy instruction and sample diary	321
Appendix 38: Instructions for saliva collection for mother and child	323
Appendix 39: History of depression questions asked as Part of the Clinical Interview.	325
Appendix 40: Unadjusted bivariate associations between infant sleep variables assessed through actigraphy, n=14.....	326
Appendix 41: Unadjusted bivariate associations between infant sleep variables assessed through maternal report, n=16	327
Appendix 42: Unadjusted bivariate associations between maternal cognitions about sleep and infant sleep	328
Appendix 43: Descriptives of CIS-R score	330
Appendix 44: Unadjusted associations between CIS-R change during pregnancy, infant temperament and sleep (2-tailed).	330
Appendix 45: The Infant Characteristics Questionnaire – fussy/difficult factor.	331

APPENDICES FOR CHAPTER 2

Appendix 1: Comparison of IBQ-R as used by Generation R (Pluess 2011 - negative emotionality) and Carey as used by ALSPAC (Ramchandani 2010 - reactivity)

	Carey (Almost never (1)- Almost Always (6)), 40 items	IBQ-R, (adapted measure see Pluess, 2011- fear, distress to limitations, recovery from distress) 3-point scale 0=never present, 1 sometime present, 2=often present, 40 items	
Feeding	1. She accepts straight away a change in place or position of feeding or person doing it 2. She takes feeding quietly with mild expression of likes and dislikes 3. She vigorously resists additional food or milk when full (spits out, clamps mouth closed, pushes spoon away etc.) 4. She resists change in feeding schedule (1 hour or more) even after 2 tries 5. She accepts new foods straight away, swallowing them promptly 6. She reacts strongly to foods, whether positively (smacks lips, laughs, squeals) or negatively (cries) 7. She continues eating solid foods without reacting to differences in taste or consistency 8. She reacts to changes in her milk (type of temperature) or if given juice instead 9. Her initial reaction is withdrawal (turns head, spits out) when consistency, flavour or temperature of solid foods is changed 10. She will take any food offered without seeming to notice the difference 11. She reacts to a disliked food even if it is mixed with a preferred one		0 items similar

	12. She requires introduction of a new food on 3 or more occasions before she will accept (swallow) it 13. She accepts changes in solid foods (type, amount, timing within 1 or 2 tries)		
Bathing and Dressing	1. She accepts her bath any time of the day without resisting it 2. She accepts regular procedures (hair brushing, face washing etc.) at any time without protest 3. She objects to being bathed in a different place or by a different person even after 2 or 3 tries 4. She displays much feeling (vigorous laughing or crying) during nappy change or dressing 5. She accepts within a few minutes a change in place of bath or person giving it 6. She is calm in the bath. Like or dislike is mildly expressed (smiles or frowns)	<u>When face was washed, how often did the baby:</u> 1. fuss or cry?	<u>Similar Items</u> Carey: 1,2,6 – IBQ-R:1
Play	1. She ignores voices or other ordinary sounds when playing with her favourite toy 2. She greets a new toy with a loud voice and much expression of feeling (whether positive or negative) 3. She plays quietly or calmly with toys (little vocal or other noises)	<u>When something the baby was playing with had to be removed, how often did s/he:</u> 1. cry or show distress for a time? 2. seem not bothered?	
Daily Activities a) Strangers	1. She reacts strongly to strangers: laughing or crying 2. She reacts mildly to meet familiar people(quiet smiles or no responses)	<u>When introduced to an unfamiliar adult, how often did the</u> 1. cling to a parent? 2. refuse to go to the unfamiliar person? 3. hang back from the adult?	Carey: 3 – IBQ-R:7

	3. She is still wary or frightened of strangers after 15 minutes 4. Her initial reaction to seeing a doctor is acceptance (smiles, coos) 5. She is shy (turns away or clings to you) on meeting another child for the first time 6. At home her initial reaction to strangers is acceptance	4. never “warm up” to the unfamiliar adult? <u>When in the presence of several unfamiliar adults, how often did the baby:</u> 5. Cling to parent 6. Cry 7. Continue to be upset for 10 minutes or longer? <u>When your baby was approached by an unfamiliar person you and s/he were out (for example, shopping) how often did the baby:</u> 8. Show distress <u>When an unfamiliar person came to your home or apartment, how often did your baby:</u> 9. Allow her/himself to be picked up without protest? 10. Cry when the visitor attempted to pick her/him up?	
b) Noises and Lights	7. She reacts mildly (just blinks or is startled briefly to a bright light such as flash bulb or sunlight let in by drawing back curtain 8. she reacts (stares or is startled) to sudden changes in lightning (flash bulbs, turning on a light) 9. She continues to react to a loud noise (hammering, barking, dog, etc.) heard several times in the same day.	<u>How often during the last week did the baby:</u> 11. startle to a loud or sudden noise?	Carey: 7,8 – IBQ-R:11
c) Nappy	10. She reacts the same as when the nappy is wet as when it is dry 11. she indicates discomfort (fussy/squirms) when she has a dirty nappy		
d) Position		<u>How often during the last week did the baby:</u> 12. protest being put in a confining place (infant seat, play pen, car seat, etc.)? 13. startle at a sudden change in body position (for example, when moved suddenly)?	

		<u>When placed on his/her back, how often did the baby:</u> 14. fuss or protest? <u>When placed in an infant seat or car seat, how often did the baby:</u> 15. show distress at first; then quiet down?	
e) Other	12. She accepts nail cutting without protest 13. Her first reaction to any new procedure (first haircut, new medicine etc.) is objection 14. she notices, looks carefully at changes in your appearance or dress (hairdo, unfamiliar clothing) 15. She reacts even to a gentle touch (is startled, wriggles, laughs, cries)	<u>How often during the last week did the baby:</u> 16. cry or show distress at a change in parents' appearance (glasses off, shower cap on, etc.)? <u>When the baby wanted something, how often did s/he:</u> 17. have tantrums (crying, screaming, face red, etc.) s/he did not get what s/he wanted? <u>When frustrated with something, how often did your baby</u> 18. Calm down within 5 minutes <u>When your baby was upset about something how often did s/he</u> 19. Stay upset for up to 10 minutes or longer 20. Stay upset for up to 20 minutes or longer 21. Soothe him/herself with other things (such as stuffed or blanket)?	Carey: 15 – IBQ-R:16
f) Novel surroundings	16. For the first few minutes in a new place or situation (new shop or home) she is fretful 17. She adjusts within 10 minutes to new surroundings (home, shop, play area)	<u>When visiting a new place, how often did the baby?</u> 22. Show distress for the first few minutes? 23. Continue to be upset for 10 minutes or longer?	Carey: 17 – IBQ-R:22 Carey: 18– IBQ-R:23
Sleeping	1. She appears bothered (cries, squirms) when first put down in a different sleeping place	<u>Before falling asleep at night during the last week, how often did the baby:</u> 1. show no fussing or crying? <u>After sleeping, how often did the baby:</u> 2. fuss or cry immediately? 3. play quietly in the crib? 4. cry if someone doesn't come within a few minutes? <u>How often did the baby:</u>	

		5. seem angry (crying and fussing) when you left her/him in the crib? 6. seem contented when left in the crib? <u>When going to bed at night how often does your baby</u> 7. Fall asleep within 10 minutes? 8. Have a hard time settling down to sleep? <u>When your baby awoke at night, how often did s/he</u> 9. Have a hard time going back to sleep? 10. Go back to sleep immediately? <u>When put down for a nap, how long did your baby?</u> 11. Stay awake for a long time? 12. Go to sleep immediately? 13. Settle down quickly? 14. Have a hard time settling down	
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Appendix 2: Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and number night awakenings at 6 months, n=8,909

	Step 1 R ² =.024					Step 2 R ² =.024					Step 3 R ² =.025					Step 4 R ² =.025				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.005	.002	.022	2.084	.037	.001	.003	.006	.431	.667	.001	.003	.006	.453	.650	.001	.003	.006	.463	.643
Gender	-.178	.021	-.088	-8.433	.000	-.178	.021	-.088	-8.440	.000	-.178	.021	-.088	-8.429	.000	-.178	.021	-.088	-8.428	.000
Ed. Qualification	.061	.009	.075	6.591	.000	.062	.009	.076	6.699	.000	.062	.009	.076	6.716	.000	.062	.009	.076	6.715	.000
Alcohol	.000	.003	.001	.060	.952	-4.192	.003	.000	-.013	.990	-5.649	.003	.000	-.018	.986	-6.815	.003	.000	-.021	.983
Smoking	-.063	.016	-.044	-3.952	.000	-.064	.016	-.045	-4.056	.000	-.064	.016	-.044	-4.010	.000	-.064	.016	-.044	-4.002	.000
Crowding	.056	.018	.034	3.127	.002	.052	.018	.032	2.931	.003	.053	.018	.033	2.948	.003	.053	.018	.033	2.958	.003
Marital Status	-.021	.008	-.031	-2.796	.005	-.020	.008	-.030	-2.683	.007	-.020	.008	-.030	-2.676	.007	-.020	.008	-.030	-2.677	.007
Maternal Age	.016	.003	.073	6.362	.000	.016	.003	.073	6.425	.000	.016	.003	.073	6.431	.000	.016	.003	.073	6.432	.000
Antenatal Depression						.028	.013	.027	2.118	.034	.011	.034	.011	.320	.749	.010	.034	.010	.305	.760
Reactivity						.012	.011	.012	1.158	.247	.062	.033	.062	1.858	.063	.062	.033	.062	1.862	.063
Depression x Reactivity											.011	.021	.017	.511	.609	.011	.021	.017	.525	.599
Depression x Gender											.005	.011	.005	.482	.630	.018	.034	.017	.526	.599
Reactivity x gender											-.033	.021	-.052	-1.563	.118	-.033	.021	-.052	-1.572	.116
Depression x Reactivity x Gender																-.008	.021	-.013	-.393	.694
	F(8,8900)=26.984,p<.001					F(10,8898)=21.93,p<.001					F(13,8895)=17.098,p<.001					F(14,8894)=16.032,p<.001				

Appendix 3: Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and total sleep time at 18 months, n=8,318

Variables	Step 1 R ² =.021					Step 2 R ² =.021					Step 3 R ² =.021					Step 4 R ² =.021				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	-.007	.002	-.033	-3.038	.002	-.006	.003	-.027	-2.014	.044	-.006	.003	-.027	-2.024	.043	-.006	.003	-.027	-2.013	.044
Gender	.109	.022	.055	5.089	.000	.110	.022	.055	5.091	.000	.109	.022	.055	5.049	.000	.109	.022	.055	5.049	.000
Ed. Qualification	.037	.009	.046	3.923	.000	.037	.009	.046	3.881	.000	.037	.009	.045	3.867	.000	.037	.009	.045	3.868	.000
Alcohol	.003	.003	.010	.875	.382	.003	.003	.010	.902	.367	.003	.003	.010	.897	.370	.003	.003	.010	.897	.370
Smoking	.084	.016	.059	5.122	.000	.085	.016	.059	5.153	.000	.084	.016	.059	5.104	.000	.084	.016	.059	5.112	.000
Crowding	.007	.018	.004	.370	.711	.008	.018	.005	.446	.656	.008	.018	.005	.420	.675	.008	.018	.005	.433	.665
Marital Status	.020	.008	.030	2.586	.010	.020	.008	.029	2.544	.011	.020	.008	.029	2.546	.011	.020	.008	.029	2.545	.011
Maternal Age	-.027	.003	-.126	-10.724	.000	-.027	.003	-.126	-10.743	.000	-.028	.003	-.127	-10.765	.000	-.028	.003	-.127	-10.764	.000
Antenatal Depression						-.010	.013	-.010	-.771	.441	.025	.035	.024	.697	.486	.024	.035	.024	.683	.495
Reactivity						-.006	.011	-.006	-.574	.566	-.055	.034	-.056	-1.623	.105	-.055	.034	-.056	-1.614	.107
Depression x Gender											-.023	.022	-.036	-1.051	.293	-.023	.022	-.035	-1.037	.300
Depression x Reactivity											-.013	.011	-.013	-1.208	.227	.000	.034	.000	-.004	.997
Reactivity x gender											.032	.022	.052	1.498	.134	.032	.022	.051	1.481	.139
Depression x Reactivity x Gender																-.009	.022	-.014	-.402	.688
	F(8,8309)=23.104,p<.001					F(10,8307)=18.565,p<.001					F(13,8304)=14.669,p<.001					F(14,8303)=13.631,p<.001				

Appendix 4: Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and number of awakenings at 18 months, n=8,310

Variables	Step 1 R ² =.013					Step 2 R ² =.013					Step 3 R ² =.014					Step 4 R ² =.014				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.015	.002	.069	6.249	.000	.014	.003	.066	4.939	.000	.014	.003	.065	4.897	.000	.014	.003	.066	4.957	.000
Gender	-.045	.022	-.022	-2.061	.039	-.045	.022	-.022	-2.060	.039	-.043	.022	-.022	-1.991	.047	-.043	.022	-.022	-1.993	.046
Ed. Qualification	-.064	.010	-.079	-6.713	.000	-.064	.010	-.079	-6.665	.000	-.064	.010	-.079	-6.690	.000	-.064	.010	-.079	-6.694	.000
Alcohol	-.002	.003	-.006	-.505	.614	-.002	.003	-.006	-.526	.599	-.002	.003	-.006	-.511	.609	-.002	.003	-.006	-.517	.606
Smoking	-.044	.017	-.030	-2.619	.009	-.044	.017	-.030	-2.641	.008	-.045	.017	-.031	-2.664	.008	-.044	.017	-.030	-2.615	.009
Crowding	.054	.018	.034	2.938	.003	.054	.019	.033	2.924	.003	.054	.019	.034	2.929	.003	.056	.019	.034	3.011	.003
Marital Status	-.012	.008	-.018	-1.515	.130	-.012	.008	-.017	-1.483	.138	-.012	.008	-.017	-1.503	.133	-.012	.008	-.017	-1.511	.131
Maternal Age	.011	.003	.048	4.080	.000	.011	.003	.048	4.065	.000	.011	.003	.048	4.095	.000	.011	.003	.048	4.102	.000
Antenatal Depression						.008	.014	.008	.609	.542	-.019	.036	-.019	-.544	.586					
Reactivity						-.011	.011	-.011	-1.021	.307	-.034	.034	-.034	-.975	.330	-.023	.036	-.022	-.640	.522
																-.031	.034	-.032	-.915	.360
Depression x Gender											.018	.022	.028	.833	.405	.020	.022	.032	.922	.356
Depression x Reactivity											.020	.011	.020	1.846	.065	.102	.035	.101	2.947	.003
Reactivity x gender											.015	.022	.025	.712	.476	.013	.022	.021	.612	.540
Depression x Reactivity x Gender																-.055	.022	-.085	-2.489	.013
	F(8,8301)=15.157,p<.001					F(10,8299)=12.281,p<.001					F(13,8296)=9.797,p<.001					F(14,8295)=9.546,p<.001				

Appendix 5: Hierarchical Regression Analysis testing the moderating effect of reactivity and gender on antenatal depression and total sleep problems at 18 months, n=8,423

Variables	Step 1 R ² =.035					Step 2 R ² =.039					Step 3 R ² =.041					Step 4 R ² =.042				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.024	.002	.113	10.416	.000	.016	.003	.072	5.491	.000	.016	.003	.072	5.461	.000	.016	.003	.072	5.524	.000
Gender	.051	.018	.080	2.844	.004	.047	.018	.074	2.640	.008	.049	.018	.076	2.735	.006	.049	.018	.076	2.734	.006
Ed. Qualification	-.052	.008	-.175	-6.433	.000	-.050	.008	-.170	-6.247	.000	-.050	.008	-.171	-6.283	.000	-.050	.008	-.171	-6.290	.000
Alcohol	.010	.003	.034	3.182	.001	.010	.003	.032	2.974	.003	.010	.003	.032	3.000	.003	.010	.003	.032	3.000	.003
Smoking	.032	.016	.022	1.992	.046	.027	.016	.018	1.659	.097	.027	.016	.019	1.664	.096	.027	.016	.019	1.711	.087
Crowding	.045	.018	.028	2.506	.012	.037	.018	.023	2.085	.037	.038	.018	.023	2.111	.035	.039	.018	.024	2.190	.029
Marital Status	.010	.006	.047	1.638	.101	.011	.006	.051	1.785	.074	.011	.006	.049	1.735	.083	.011	.006	.049	1.722	.085
Maternal Age	-.019	.002	-.086	-7.717	.000	-.019	.002	-.085	-7.593	.000	-.018	.002	-.084	-7.526	.000	-.018	.002	-.084	-7.526	.000
Antenatal Depression						.080	.013	.079	6.023	.000	.028	.035	.028	.801	.423	.024	.035	.024	.696	.486
Reactivity						-.018	.011	-.018	-1.659	.097	.004	.034	.004	.128	.899	.006	.034	.006	.188	.851
Depression x Gender											.034	.022	.053	1.581	.114	.036	.022	.056	1.679	.093
Depression x Reactivity											.033	.011	.032	3.016	.003	.117	.034	.116	3.460	.001
Reactivity x gender											.014	.021	.022	.649	.517	.016	.021	.025	.750	.453
Depression x Reactivity x Gender																.057	.022	.089	2.637	.008
	F(8,8415)=37.772,p<.001					F(10,8413)=34.521,p<.001					F(13,8410)=27.525,p<.001					F(14,8409)=26.074,p<.001				

Appendix 6: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and total sleep time at 30 months of age, n=7,816

\	Step 1 R ² =.027					Step 2 R ² =.027					Step 3 R ² =.028					Step 4 R ² =.028				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.006	.002	.028	2.458	.014	.006	.003	.028	2.017	.044	.006	.003	.028	2.029	.042	.006	.003	.028	2.047	.041
Gender	-.158	.022	-.079	-7.104	.000	-.158	.022	-.079	-7.105	.000	-.156	.022	-.078	-7.014	.000	-.156	.022	-.078	-7.013	.000
Ed. Qualification	-.012	.010	-.015	-1.231	.218	-.012	.010	-.015	-1.234	.217	-.012	.010	-.014	-1.181	.238	-.012	.010	-.014	-1.182	.237
Alcohol	.008	.003	.027	2.388	.017	.008	.003	.027	2.388	.017	.008	.003	.027	2.387	.017	.008	.003	.027	2.389	.017
Smoking	-.045	.017	-.031	-2.654	.008	-.045	.017	-.031	-2.647	.008	-.044	.017	-.031	-2.595	.009	-.044	.017	-.030	-2.581	.010
Crowding	-.028	.019	-.017	-1.482	.138	-.028	.019	-.017	-1.484	.138	-.027	.019	-.017	-1.438	.150	-.027	.019	-.017	-1.410	.158
Marital Status	-.020	.008	-.030	-2.530	.011	-.020	.008	-.030	-2.528	.011	-.021	.008	-.030	-2.554	.011	-.021	.008	-.030	-2.554	.011
Maternal Age	.029	.003	.133	11.062	.000	.029	.003	.133	11.062	.000	.029	.003	.134	11.116	.000	.029	.003	.134	11.115	.000
Antenatal Depression						-.001	.014	-.001	-.065	.948	-.074	.036	-.073	-2.034	.042	-.075	.036	-.074	-2.049	.040
Reactivity						.004	.011	.004	.312	.755	.062	.035	.062	1.768	.077	.063	.035	.063	1.787	.074
Depression x Gender											.049	.023	.075	2.154	.031	.049	.023	.076	2.167	.030
Depression x Reactivity											.021	.011	.021	1.834	.067	.047	.036	.046	1.324	.185
Reactivity x gender											-.039	.022	-.061	-1.728	.084	-.039	.022	-.062	-1.756	.079
Depression x Reactivity x Gender																-.018	.023	-.027	-.781	.435
	F(8,7807)=26.945,p<.001					F(10,7805)=21.561,p<.001					F(13,7802)=17.468,p<.001					F(14,7801)=16.236,p<.001				

Appendix 7 Hierarchical Regression Analysis testing the moderating effect reactivity on antenatal depression and number of awakenings at 30 months, n=7,877

Variables	Step 1 R ² =.007					Step 2 R ² =.007					Step 3 R ² =.008					Step 4 R ² =.009				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.008	.002	.036	3.138	.002	.005	.003	.021	1.513	.130	.004	.003	.020	1.449	.147	.005	.003	.021	1.509	.131
Gender	-.037	.022	-.019	-1.669	.095	-.038	.022	-.019	-1.678	.093	-.037	.022	-.018	-1.639	.101	-.037	.022	-.018	-1.643	.100
Ed. Qualification	-.056	.010	-.069	-5.698	.000	-.055	.010	-.068	-5.594	.000	-.056	.010	-.068	-5.621	.000	-.056	.010	-.068	-5.623	.000
Alcohol	.000	.003	.001	.075	.940	4.670E-5	.003	.000	.013	.989	.000	.003	.000	.033	.973	6.423E-5	.003	.000	.018	.985
Smoking	-.034	.017	-.023	-1.957	.050	-.035	.017	-.024	-2.049	.040	-.036	.017	-.025	-2.090	.037	-.035	.017	-.024	-2.049	.041
Crowding	.007	.019	.004	.371	.711	.004	.019	.003	.228	.819	.005	.019	.003	.239	.811	.006	.019	.004	.316	.752
Marital Status	-.008	.008	-.012	-.987	.324	-.007	.008	-.011	-.883	.377	-.007	.008	-.011	-.887	.375	-.007	.008	-.011	-.891	.373
Maternal Age	.008	.003	.034	2.841	.005	.008	.003	.035	2.870	.004	.008	.003	.035	2.884	.004	.008	.003	.035	2.881	.004
 Antenatal Depression						.028	.014	.027	1.962	.050	.040	.037	.039	1.075	.283	.038	.037	.037	1.025	.305
Reactivity						-.001	.011	-.001	-.058	.954	-.046	.035	-.045	-1.283	.200	-.043	.036	-.043	-1.203	.229
 Depression x Gender											-.008	.023	-.012	-.346	.730	-.007	.023	-.011	-.300	.765
Depression x Reactivity											.023	.012	.023	2.010	.045	.103	.036	.100	2.824	.005
Reactivity x gender											.031	.023	.048	1.367	.172	.028	.023	.045	1.255	.210
Depression x Reactivity x Gender																-.053	.023	-.082	-2.305	.021
	F(8,7868)=6.608,p<.001					F(10,7866)=5.680,p<.001					F(13,7863)=4.822,p<.001					F(14,7862)=4.859,p<.001				

Appendix 8: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and total sleep problems at 30 months
n=7,692

Variables	Step 1 R ² =.045					Step 2 R ² =.052					Step 3 R ² =.052					Step 4 R ² =.052				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.030	.002	.138	12.221	.000	.018	.003	.084	6.093	.000	.018	.003	.083	6.035	.000	.018	.003	.083	6.059	.000
Gender	-.038	.022	-.019	-1.700	.089	-.039	.022	-.019	-1.736	.083	-.036	.022	-.018	-1.616	.106	-.036	.022	-.018	-1.621	.105
Ed. Qualification	-.068	.010	-.083	-6.926	.000	-.064	.010	-.079	-6.570	.000	-.065	.010	-.079	-6.593	.000	-.065	.010	-.079	-6.591	.000
Alcohol	.011	.003	.034	3.036	.002	.010	.003	.032	2.869	.004	.010	.003	.033	2.889	.004	.010	.003	.033	2.888	.004
Smoking	.046	.017	.032	2.700	.007	.040	.017	.028	2.343	.019	.039	.017	.027	2.299	.022	.040	.017	.027	2.318	.020
Crowding	-.016	.019	-.010	-.845	.398	-.026	.019	-.016	-1.350	.177	-.026	.019	-.016	-1.355	.175	-.025	.019	-.015	-1.319	.187
Marital Status	-.026	.008	-.037	-3.151	.002	-.023	.008	-.033	-2.799	.005	-.023	.008	-.033	-2.830	.005	-.023	.008	-.033	-2.833	.005
Maternal Age	-.017	.003	-.077	-6.386	.000	-.017	.003	-.076	-6.328	.000	-.017	.003	-.076	-6.294	.000	-.017	.003	-.076	-6.295	.000
Antenatal Depression						.103	.014	.102	7.407	.000	.054	.036	.053	1.467	.142	.053	.037	.052	1.441	.150
Reactivity						-.012	.011	-.012	-1.039	.299	-.064	.035	-.064	-1.812	.070	-.062	.035	-.062	-1.777	.076
Depression x Gender											.034	.023	.052	1.491	.136	.034	.023	.053	1.512	.131
Depression x Reactivity											.017	.011	.017	1.487	.137	.052	.036	.051	1.445	.148
Reactivity x gender											.035	.022	.056	1.590	.112	.034	.022	.054	1.540	.124
Depression x Reactivity x Gender																-.023	.023	-.036	-1.026	.305
	F(8,7663)=45.817,p<.001					F(10,7658)=42.771,p<.001					F(13,7658)=33.443,p<.001					F(14,7657)=31.130,p<.001				

Appendix 9: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and total sleep duration at 6 months n=2,241

Variables	Step 1 R ² =.009					Step 2 R ² =.010					Step 3 R ² =.011					Step 4 R ² =.011				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	-.019	.021	-.019	-.900	.368	-.004	.024	-.004	-.179	.858	-.005	.024	-.005	-.214	.831	-.005	.024	-.005	-.214	.831
Gender	.015	.021	.015	.694	.488	.013	.021	.013	.623	.533	.013	.021	.013	.596	.551	.013	.021	.013	.591	.555
Ed. Qualification	.018	.022	.021	.848	.397	.019	.022	.021	.866	.386	.019	.022	.022	.879	.380	.019	.022	.022	.877	.380
Alcohol	.089	.047	.043	1.866	.062	.091	.048	.044	1.923	.055	.091	.048	.044	1.912	.056	.091	.048	.044	1.912	.056
Smoking	.082	.054	.034	1.530	.126	.088	.054	.036	1.635	.102	.089	.054	.036	1.647	.100	.089	.054	.036	1.647	.100
Crowding	-.021	.025	-.019	-.854	.393	-.022	.025	-.019	-.866	.387	-.022	.025	-.019	-.855	.393	-.022	.025	-.019	-.855	.392
Marital Status	-.240	.080	-.066	-3.021	.003	-.236	.080	-.065	-2.963	.003	-.235	.080	-.065	-2.946	.003	-.235	.080	-.065	-2.945	.003
Maternal Age	-.002	.005	-.010	-.407	.684	-.002	.005	-.011	-.455	.649	-.003	.005	-.011	-.477	.633	-.003	.005	-.011	-.477	.633
Antenatal Depression						-.034	.024	-.034	-1.421	.155	-.036	.024	-.036	-1.482	.139	-.036	.024	-.036	-1.483	.138
Reactivity						.012	.022	.012	.540	.590	.012	.022	.012	.547	.584	.012	.023	.012	.549	.583
Depression x Reactivity											-.001	.022	-.001	-.064	.949	-.001	.023	-.001	-.049	.961
Depression x Gender											-.016	.022	-.015	-.715	.475	-.016	.022	-.015	-.717	.474
Reactivity x gender											-.006	.022	-.006	-.284	.776	-.006	.022	-.006	-.284	.776
Depression x Reactivity x Gender																.001	.023	.001	.054	.957
	F(8,2232)=2.605,p=.008					F(10,2230)=2.325,p=.010					F(13,2227)=1.835,p=.033					F(14,2226)=1.703,p=.049				

Appendix 10: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and number of night awakenings at 6 months
n=2,169

Variables	Step 1 R ² =.024					Step 2 R ² =.024					Step 3 R ² =.027					Step 4 R ² =.027				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.000	.021	.000	.008	.994	-.011	.024	-.011	-.462	.644	-.008	.024	-.008	-.347	.729	-.008	.024	-.008	-.347	.728
Gender	-.109	.021	-.109	-5.106	.000	-.110	.021	-.110	-5.124	.000	-.110	.021	-.110	-5.146	.000	-.109	.021	-.109	-5.062	.000
Ed. Qualification	.018	.022	.020	.820	.412	.019	.022	.021	.856	.392	.016	.022	.018	.734	.463	.016	.022	.019	.751	.453
Alcohol	-.050	.048	-.024	-1.051	.293	-.050	.048	-.024	-1.043	.297	-.051	.048	-.025	-1.069	.285	-.053	.048	-.026	-1.100	.271
Smoking	-.078	.054	-.032	-1.440	.150	-.082	.054	-.034	-1.510	.131	-.082	.054	-.034	-1.512	.131	-.083	.055	-.034	-1.523	.128
Crowding	.087	.025	.076	3.441	.001	.086	.026	.074	3.354	.001	.084	.026	.073	3.303	.001	.085	.026	.073	3.322	.001
Marital Status	.094	.080	.026	1.164	.244	.088	.081	.024	1.086	.278	.085	.081	.023	1.049	.294	.085	.081	.023	1.051	.293
Maternal Age	.014	.005	.061	2.551	.011	.014	.005	.063	2.642	.008	.015	.005	.065	2.699	.007	.015	.005	.065	2.704	.007
 Antenatal Depression						.024	.025	.023	.956	.339	.023	.025	.022	.889	.374	.023	.025	.023	.921	.357
Reactivity						.010	.022	.009	.433	.665	.011	.023	.011	.506	.613	.010	.023	.010	.454	.650
 Depression x Reactivity											.027	.022	.026	1.191	.234	.021	.023	.020	.892	.373
Depression x Gender											.030	.022	.030	1.375	.169	.033	.022	.032	1.495	.135
Reactivity x gender											-.025	.022	-.024	-1.129	.259	-.025	.022	-.024	-1.129	.259
 Depression x Reactivity x Gender																-.024	.023	-.023	-1.041	.298
	F(8,2160)=6.637,p<.001					F(10,2158)=5.419,p<.001					F(13,2155)=4.518,p<.001					F(14,2154)=4.273,p<.001				

Appendix 11: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and total sleep duration at 24 months
n=1,898

Variables	Step 1 R ² =.024					Step 2 R ² =.025					Step 3 R ² =.026					Step 4 R ² =.029				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	-.033	.024	-.032	-1.407	.160	-.018	.027	-.018	-.670	.503	-.014	.027	-.013	-.507	.612	-.014	.027	-.013	-.502	.616
Gender	.092	.023	.092	4.021	.000	.092	.023	.092	4.013	.000	.093	.023	.093	4.045	.000	.090	.023	.090	3.909	.000
Ed. Qualification	.036	.024	.039	1.504	.133	.036	.024	.039	1.500	.134	.036	.024	.038	1.469	.142	.036	.024	.039	1.482	.139
Alcohol	.160	.052	.077	3.078	.002	.160	.052	.076	3.064	.002	.158	.052	.076	3.028	.002	.159	.052	.076	3.043	.002
Smoking	.053	.059	.021	.894	.372	.059	.060	.024	.992	.321	.060	.060	.024	1.002	.316	.060	.060	.025	1.038	.299
Crowding	.043	.028	.037	1.558	.119	.045	.028	.038	1.604	.109	.044	.028	.037	1.578	.115	.043	.028	.037	1.543	.123
Marital Status	-.222	.093	-.056	-2.402	.016	-.217	.093	-.055	-2.332	.020	-.220	.093	-.056	-2.370	.018	-.223	.093	-.056	-2.398	.017
Maternal Age	-.020	.006	-.085	-3.404	.001	-.020	.006	-.087	-3.452	.001	-.020	.006	-.086	-3.390	.001	-.020	.006	-.086	-3.406	.001
Antenatal Depression						-.032	.028	-.031	-1.164	.244	-.033	.028	-.031	-1.190	.234	-.032	.028	-.030	-1.152	.250
Reactivity						-.002	.025	-.002	-.071	.943	-.001	.025	-.001	-.029	.977	.004	.025	.004	.180	.857
Depression x Reactivity											.012	.025	.011	.463	.644	.033	.027	.031	1.232	.218
Depression x Gender											.038	.025	.035	1.530	.126	.034	.025	.032	1.387	.165
Reactivity x gender											-.002	.024	-.002	-.075	.940	.001	.024	.001	.046	.963
Depression x Reactivity x Gender																.057	.027	.053	2.120	.034
	F(8,1888)=5.909,p<.001					F(10,1886)=4.861,p<.001					F(13,1883)=3.929,p<.001					F(14,1882)=3.976,p<.001				

Appendix 12: Hierarchical Regression Analysis testing the moderating effect of reactivity on antenatal depression and number of night awakenings at 24months n=1,974

Variables	Step 1 R ² =.013					Step 2 R ² =.016					Step 3 R ² =.017					Step 4 R ² =.018				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.033	.023	.032	1.401	.161	.001	.026	.001	.056	.955	.003	.027	.003	.098	.922	.003	.027	.003	.102	.919
Gender	-.030	.022	-.030	-1.333	.183	-.029	.023	-.029	-1.283	.200	-.029	.023	-.029	-1.296	.195	-.027	.023	-.027	-1.198	.231
Ed. Qualification	-.062	.023	-.069	-2.670	.008	-.063	.023	-.069	-2.701	.007	-.063	.023	-.070	-2.710	.007	-.063	.023	-.070	-2.717	.007
Alcohol	-.047	.051	-.023	-.929	.353	-.050	.051	-.024	-.972	.331	-.050	.051	-.024	-.970	.332	-.050	.051	-.024	-.989	.323
Smoking	.015	.058	.006	.256	.798	-5.246	.058	.000	-.001	.999	-1.418	.058	.000	.000	1.000	.000	.058	.000	-.006	.995
Crowding	.011	.027	.010	.418	.676	.009	.027	.008	.343	.731	.009	.027	.007	.319	.750	.010	.027	.009	.366	.714
Marital Status	.221	.089	.058	2.494	.013	.211	.089	.055	2.370	.018	.211	.089	.055	2.369	.018	.212	.089	.055	2.383	.017
Maternal Age	.011	.006	.049	1.971	.049	.012	.006	.052	2.088	.037	.012	.006	.051	2.056	.040	.012	.006	.051	2.064	.039
Antenatal Depression						.068	.027	.066	2.523	.012	.070	.027	.067	2.578	.010	.071	.027	.068	2.588	.010
Reactivity						-.009	.024	-.009	-.383	.702	-.009	.024	-.008	-.362	.718	-.011	.024	-.011	-.469	.639
Depression x Reactivity											-.015	.024	-.014	-.604	.546	-.027	.026	-.025	-1.041	.298
Depression x Gender											.014	.024	.013	.594	.552	.017	.024	.016	.712	.476
Reactivity x gender											-.007	.024	-.006	-.278	.781	-.007	.024	-.007	-.315	.752
Depression x Reactivity x Gender																-.035	.026	-.033	-1.367	.172
	F(8,1965)=3.202,p=.001					F(10,1963)=3.233,p<.001					F(13,1960)=2.543,p=.002					F(14,1959)=2.496,p=.002				

APPENDICES FOR CHAPTER 3

Appendix 13: Unadjusted association for sleep items for participants with genetic data

	Total time asleep (hrs.)	No. of awakenings per night	No. hours asleep at night	NO of Times CH Wakes During Night	Sleep Problems at 18 months	Total sleep time- 30 months	Frequency child wakes in night	Sleep Problems at 30 months
Total time asleep (hrs.)	—	-.212**	.358**	-.222**	-.266**	-.269**	-.160**	-.160**
		.000	.000	.000	.000	.000	.000	.000
No. of awakenings per night		—	-.111**	.222**	.168**	.060**	.122**	.077**
			.000	.000	.000	.000	.000	.000
No. hours asleep at night			—	-.247**	-.314**	-.528**	-.187**	-.198**
				.000	.000	.000	.000	.000
NO of Times CH Wakes During Night				—	.451**	.173**	.455**	.257**
					.000	.000	.000	.000
Sleep Problems at 18 months					—	.185**	.294**	.442**
						.000	.000	.000
Total sleep time- 30 months						—	.184**	.239**
							.000	.000
Frequency child wakes in night							—	.369**
								.000
Sleep Problems at 30 months								—

**, Correlation is significant at the 0.01 level (2-tailed).

Appendix 14: Unadjusted associations between sleep variables, antenatal depression, 5-HTTLPR and covariates at 6 months (n=4229)

		Sleep Variable		Moderator	Depression Scores	
		Sleep Duration	Awakenings	5-HTTLPR	Antenatal depression	Postnatal Depression
Sleep Variable	Sleep Duration	—				
	Number of awakenings	-.242**(.000)	—			
Moderator	5-HTTLPR	-.011(.470)	-.016(.304)	—		
Depression Scores	Antenatal depression	-.006(.672)	.016(.303)	.028(.071)	—	
	Postnatal Depression	-.043**(.000)	.015(.332)	.022(.141)	.573**(.000)	—
Covariates	Ed. Qualification	-.008(.623)	.084**(.000)	-.020(.184)	-.115**(.000)	.053**(.000)
	Smoking	.030(.051)	-.038*(.012)	.019(.223)	.136**(.000)	.089**(.000)
	Marital Status	.027(.077)	.011(.461)	.001(.957)	-.100**(.000)	-.030*(.049)
	Crowding	.034*(.028)	.013(.386)	-.004(.803)	.117**(.000)	.064**(.000)
	Alcohol	.000(.976)	-.007(.630)	.013(.391)	.070**(.000)	.054**(.000)
	Maternal Age	-.073**(.000)	.070**(.000)	-.016(.293)	-.045**(.003)	.027(.077)

** . Correlation is significant at the 0.01 level. * . Correlation is significant at the 0.05 level

Appendix 15: Unadjusted associations between variables at 18 month (n=4,179)

Sleep Variables				Moderator		
	Sleep Duration	Awakenings	Sleep Problems	5-HTTLPR	Antenatal Depression	Postnatal Depression
Sleep Variables	Sleep Duration	—				
	Awakenings	-.243**(.000)	—			
	Sleep Problems	-.315**(.000)	.439**(.000)	—		
Moderator	5-HTTLPR	-.009(.572)	.017(.275)	.009(.538)	—	
	Antenatal Depression	-.025(.111)	.054**(.000)	.138**(.000)	.032*(.037)	—
Depression Scores	Postnatal Depression	-.028(.069)	.051**(.001)	.117**(.000)	.018(.232)	.575**(.000)
Covariates	Crowding	.011(.495)	-.077**(.000)	.132**(.000)	-.020(.198)	-.107**(.000)
	Ed Qual.	.058**(.000)	.002(.880)	.041**(.007)	.016(.306)	.138**(.000)
	Smoking	-.008(.585)	.009(.579)	.049**(.001)	-.009(.538)	-.080**(.000)
	Marital status	.004(.775)	.054**(.000)	.059**(.000)	.001(.925)	.112**(.000)
	Alcohol	.019(.212)	-.040**(.010)	-.009(.576)	.016(.303)	.062**(.000)
	Maternal Age	-.131**(.000)	.019(.208)	.075**(.000)	-.011(.473)	-.037*(.016)
**. Correlation is significant at the 0.01 level. *. Correlation is significant at the 0.05 level						

Appendix 16: Unadjusted associations between variables at 30 months (n=4,025)

		Sleep Variables			Moderator	Predictor	
		Total time	sleepNight awakenings	Sleep Problems	5-HTTLPR	Antenatal Depression	Postnatal Depression
Sleep Variables	Total sleep time	——					
	Awakenings	.190**(.000)	——				
	Sleep Problems	.253**(.000)	.377**(.000)	——			
Moderator	5-HTTLPR	-.006(.688)	.004(.779)	.001(.942)	——		
Depression Scores	Antenatal Depression	-.002(.886)	.029(.069)	.149**(.000)	.033*(.040)	——	
	Postnatal Depression	.015(.354)	.033*(.035)	.136**(.000)	.028(.077)	.577**(.000)	——
Covariates	Ed Qual.	.017(.272)	-.065**(.000)	-.125**(.000)	-.030(.063)	-.107**(.000)	-.053**(.001)
	Smoking	-.042**(.009)	.011(.484)	.065**(.000)	.010(.538)	.143**(.000)	.090**(.000)
	Marital Status	.035*(.026)	-.004(.779)	-.040*(.011)	.001(.954)	-.091**(.000)	-.024(.126)
	Crowding	-.032*(.041)	.032*(.043)	.043**(.007)	.008(.593)	.114**(.000)	.061**(.000)
	Alcohol	.043**(.007)	.001(.972)	.010(.525)	.020(.207)	.061**(.000)	.060**(.000)
	Maternal Age	.153**(.000)	.010(.545)	-.082**(.000)	-.011(.504)	-.043**(.006)	.028(.081)

** . Correlation is significant at the 0.01 level. * . Correlation is significant at the 0.05 level

Appendix 17: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 6 months, n=4,119.

Variables	Step 1 R ² =.10					Step 2 R ² =.011					Step 3 R ² =.011					Step 4 R ² =.012				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	-.016	.007	-.036	-2.312	.021	-.023	.008	-.051	-2.714	.007	-.023	.008	-.051	.879	.380	-.023	.008	-.051	-2.702	.007
Gender	.080	.031	.040	2.601	.009	.080	.031	.040	2.599	.009	.083	.094	.042	1.253	.210	.078	.094	.039	.827	.409
Ed. Qualification	.034	.028	.020	1.214	.225	.036	.028	.022	1.283	.200	.035	.028	.021	-.118	.906	.035	.028	.021	1.272	.203
Alcohol	-.001	.010	-.002	-.126	.899	-.001	.010	-.002	-.150	.881	-.001	.010	-.002	2.089	.037	-.001	.010	-.002	-.135	.893
Smoking	.113	.053	.035	2.144	.032	.109	.053	.034	2.078	.038	.110	.053	.034	1.948	.051	.110	.053	.034	2.088	.037
Crowding	.111	.054	.033	2.062	.039	.106	.054	.032	1.950	.051	.106	.054	.032	3.173	.002	.105	.054	.031	1.935	.053
Marital Status	.074	.024	.050	3.086	.002	.077	.024	.052	3.176	.002	.077	.024	.052	-4.063	.000	.077	.024	.052	3.205	.001
Maternal Age	-.030	.007	-.068	-4.089	.000	-.030	.007	-.067	-4.067	.000	-.030	.007	-.067	1.616	.106	-.030	.007	-.067	-4.059	.000
Antenatal Depression						.012	.008	.028	1.459	.145	.033	.021	.080	-1.062	.288	.032	.021	.078	1.569	.117
5-HTTLPR						-.044	.044	-.016	-1.010	.313	-.047	.044	-.017	-.034	.973	-.047	.044	-.017	-1.065	.287
Depression x Gender											-.001	.044	-.002	-1.145	.252	.000	.044	.001	.011	.991
Depression x 5-HTTLPR											-.011	.009	-.055	-.109	.913	-.010	.009	-.053	-1.091	.275
5-HTTLPR x Gender											-.001	.006	-.002			-.020	.020	-.047	-.976	.329
Depression x 5-HTTLPR x Gender																.009	.009	.048	.993	.321
	F(8,4110)=5.38 , p<.001					F(10, 4108)=4.61 , p<.001					F(13,4105)=3.65 , p<.001					F(14,4104)= 3.46, p<.001				

Appendix 18: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and number nighttime awakenings at 6 months, n=4,229

Variables	Step 1 R2=.018					Step 2 R2=.019					Step 3 R2=.020					Step 4 R2=.020				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.006	.005	.021	1.342	.180	.000	.006	.001	.068	.946	.000	.006	.001	.046	.963	.000	.006	.001	.032	.974
Gender	-.092	.020	-.069	-4.517	.000	-.092	.020	-.069	-4.513	.000	-.095	.062	-.071	-1.520	.129	-.090	.063	-.067	-1.436	.151
Ed. Qualification	.079	.018	.071	4.309	.000	.081	.018	.073	4.401	.000	.082	.018	.073	4.420	.000	.081	.018	.072	4.391	.000
Alcohol	-.004	.007	-.008	-.527	.598	-.004	.007	-.009	-.570	.569	-.004	.007	-.009	-.571	.568	-.004	.007	-.009	-.551	.582
Smoking	-.086	.035	-.040	-2.476	.013	-.090	.035	-.042	-2.583	.010	-.090	.035	-.042	-2.590	.010	-.090	.035	-.042	-2.581	.010
Crowding	.082	.036	.036	2.294	.022	.078	.036	.035	2.168	.030	.078	.036	.035	2.183	.029	.079	.036	.035	2.198	.028
Marital Status	-.017	.016	-.017	-1.072	.284	-.016	.016	-.016	-.976	.329	-.016	.016	-.016	-1.014	.311	-.017	.016	-.017	-1.077	.281
Maternal Age	.019	.005	.062	3.794	.000	.019	.005	.063	3.838	.000	.019	.005	.063	3.865	.000	.019	.005	.063	3.865	.000
Antenatal Depression						.010	.005	.035	1.871	.061	.002	.014	.006	.123	.902	.003	.014	.011	.224	.823
5-HTTLPR						-.016	.029	-.009	-.565	.572	-.016	.029	-.008	-.531	.596	-.016	.029	-.008	-.531	.596
Depression x Gender											.002	.029	.003	.056	.955	.000	.029	-.001	-.017	.987
Depression x 5-HTTLPR											.004	.006	.033	.683	.495	.004	.006	.028	.577	.564
5-HTTLPR x Gender											.005	.004	.019	1.218	.223	.026	.013	.091	1.902	.057
Depression x 5-HTTLPR x Gender																-.010	.006	-.076	-1.596	.111
	F(8,4220)= 9.83, p<.001					F(10,4218)=8.25 , p<.001					F(13,4215)=6.50 , p<.001					F(14,4214)=6.21 , p<.001				

Appendix 19: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 18 months, n=4,131.

Variables	Step 1 R2=.025					Step 2 R2=.026					Step 3 R2=.027					Step 4 R2=.027				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	-.004	.003	-.018	-1.139	.255	-.001	.004	-.005	-.286	.775	-.001	.004	-.005	-.251	.802	-.001	.004	-.005	-.247	.805
Gender	.061	.015	.060	3.922	.000	.060	.015	.060	3.911	.000	.133	.047	.133	2.825	.005	.132	.047	.131	2.787	.005
Ed. Qualification	.054	.014	.064	3.841	.000	.053	.014	.063	3.767	.000	.053	.014	.063	3.781	.000	.053	.014	.063	3.791	.000
Alcohol	.009	.005	.029	1.862	.063	.010	.005	.030	1.920	.055	.010	.005	.030	1.931	.054	.010	.005	.030	1.924	.054
Smoking	.093	.026	.058	3.560	.000	.096	.026	.060	3.647	.000	.095	.026	.059	3.630	.000	.095	.026	.059	3.622	.000
Crowding	.002	.027	.001	.087	.930	.004	.027	.002	.144	.885	.004	.027	.003	.166	.868	.004	.027	.003	.162	.871
Marital Status	.016	.012	.021	1.296	.195	.015	.012	.020	1.259	.208	.015	.012	.020	1.262	.207	.016	.012	.021	1.283	.199
Maternal Age	-.031	.004	-.135	-8.258	.000	-.031	.004	-.136	-8.297	.000	-.031	.004	-.137	-8.334	.000	-.031	.004	-.137	-8.332	.000
Antenatal Depression						-.005	.004	-.022	-1.134	.257	-.001	.010	-.003	-.059	.953	-.001	.010	-.005	-.101	.919
5-HTTLPR						-.023	.022	-.016	-1.057	.291	-.025	.022	-.018	-1.154	.249	-.025	.022	-.018	-1.151	.250
Depression x Gender											-.036	.022	-.077	-1.643	.100	-.036	.022	-.076	-1.611	.107
Depression x 5-HTTLPR											-.002	.005	-.021	-.441	.659	-.002	.005	-.019	-.396	.692
5-HTTLPR x Gender											-.002	.003	-.011	-.738	.461	-.009	.010	-.041	-.842	.400
Depression x 5-HTTLPR x Gender																.003	.005	.031	.639	.523
	F(8,4122)= 13.27, p<.001					F(10,4120)=10.86 , p<.001					F(13,4117)=8.62 , p<.001					F(14,4116)=8.04 , p<.001				

Appendix 20: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and number nighttime awakenings at 18 months, n=4,133.

Variables	Step 1 R2=.015					Step 2 R2=.016					Step 3 R2=.017					Step 4 R2=.017				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.010	.004	.044	2.830	.005	.006	.004	.026	1.395	.163	.006	.004	.026	1.382	.167	.006	.004	.026	1.377	.168
Gender	-.009	.016	-.008	-.531	.595	-.008	.016	-.008	-.521	.602	.003	.050	.003	.059	.953	.006	.050	.006	.126	.899
Ed. Qualification	-.075	.015	-.085	-	.000	-.074	.015	-.083	-4.966	.000	-.073	.015	-.083	-4.953	.000	-.074	.015	-.083	-4.979	.000
				5.074																
Alcohol	-.013	.005	-.037	-	.017	-.013	.005	-.038	-2.444	.015	-.013	.005	-.038	-2.433	.015	-.013	.005	-.038	-2.418	.016
				2.380																
Smoking	-.026	.028	-.015	-.946	.344	-.030	.028	-.017	-1.062	.288	-.029	.028	-.017	-1.057	.291	-.029	.028	-.017	-1.053	.292
Crowding	.097	.029	.055	3.383	.001	.094	.029	.053	3.291	.001	.094	.029	.053	3.301	.001	.095	.029	.053	3.307	.001
Marital Status	.002	.013	.003	.195	.846	.003	.013	.004	.255	.798	.003	.013	.004	.220	.826	.002	.013	.003	.178	.859
Maternal Age	.011	.004	.045	2.752	.006	.011	.004	.046	2.805	.005	.011	.004	.047	2.832	.005	.011	.004	.047	2.823	.005
Antenatal Depression						.007	.004	.031	1.625	.104	.003	.011	.013	.265	.791	.004	.011	.017	.336	.737
5-HTTLPR						.022	.023	.015	.950	.342	.022	.023	.015	.962	.336	.022	.023	.015	.960	.337
Depression x Gender											-.005	.023	-.011	-.227	.820	-.007	.023	-.013	-.286	.775
Depression x 5-HTTLPR											.002	.005	.021	.426	.670	.002	.005	.017	.347	.728
5-HTTLPR x Gender											.005	.003	.020	1.310	.190	.017	.011	.078	1.617	.106
Depression x 5-HTTLPR x Gender																-.006	.005	-.061	-1.264	.206
	F(8,4124)=8.03 , p<.001					F(10,4122)=6.78 , p<.001					F(13,4119)=5.37 , p<.001					F(14,4118)=5.1 , p<.001				

Appendix 21: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep problems at 18 months, n=4,179

Variables	Step 1 R ² =.034					Step 2 R ² =.040					Step 3 R ² =.041					Step 4 R ² =.041				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.046	.006	.112	7.271	.000	.025	.008	.061	3.255	.001	.025	.008	.061	3.254	.001	.025	.008	.061	3.253	.001
Gender	-	.028	-	-.919	.358	-	.028	-	-.899	.369	.104	.086	.056	1.212	.226	.105	.086	.056	1.217	.224
	.026		.014			.025		.014												
Ed. Qualification	-	.025	-	-	.000	-	.025	-	-	.000	-	.025	-	-	.000	-	.025	-	-	.000
	.178		.115	6.986		.171		.110	6.732		.171		.110	6.697		.171		.110	6.698	
Alcohol	-	.009	-	-.370	.711	-	.009	-	-.526	.599	-	.009	-	-.508	.611	-	.009	-	-.506	.613
	.003		.006			.005		.008			.005		.008			.005		.008		
Smoking	-	.048	-	-.501	.617	-	.048	-	-.838	.402	-	.048	-	-.845	.398	-	.048	-	-.843	.399
	.024		.008			.040		.014			.040		.014			.040		.014		
Crowding	.081	.049	.026	1.639	.101	.067	.049	.022	1.358	.175	.068	.049	.022	1.389	.165	.068	.049	.022	1.389	.165
Marital Status	-	.022	-	-	.036	-	.022	-	-	.056	-	.022	-	-	.050	-	.022	-	-	.050
	.046		.033	2.092		.042		.030	1.912		.043		.031	1.960		.043		.031	1.963	
Maternal Age	-	.007	-	-	.061	-	.007	-	-	.081	-	.007	-	-	.084	-	.007	-	-	.084
	.013		.030	1.873		.012		.028	1.742		.012		.028	1.726		.012		.028	1.726	
Antenatal Depression						.035	.007	.091	4.817	.000	.031	.019	.079	1.624	.104	.031	.019	.079	1.629	.103
5-HTTLPR						.012	.040	.005	.299	.765	.010	.040	.004	.248	.804	.010	.040	.004	.248	.804
Depression x Gender											-	.040	-	-	.114	-	.040	-	-	.113
											.063		.073	1.579		.064		.073	1.584	
Depression x 5-HTTLPR											.003	.009	.014	.294	.769	.002	.009	.014	.286	.775
5-HTTLPR x Gender											.008	.006	.021	1.383	.167	.011	.019	.027	.576	.565
Depression x 5-HTTLPR x Gender																-	.009	-	-.139	.889
																.001		.007		
	F(8,4170)=18.57 , p<.001					F(10,4168)=17.27 , p<.001					F(13,4165)=13.62 , p<.001					F(14,4164)=12.65 , p<.001				

Appendix 22: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 30 months, n=4,131

Variables	Step 1 R ² =.034					Step 2 R ² =.034					Step 3 R ² =.035					Step 4 R ² =.035				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	8.185	11.962	.011	.684	.494	6.652	14.518	.009	.458	.647	6.138	14.519	.008	.423	.673	6.166	14.521	.008	.425	.671
Gender	-300.644	53.254	-.088	-5.645	.000	-300.615	53.268	-.088	-5.643	.000	-419.453	162.627	-.123	-2.579	.010	-415.112	162.913	-.121	-2.548	.011
Ed. Qualification	-116.722	48.109	-.041	-2.426	.015	-116.082	48.190	-.041	-2.409	.016	-116.316	48.216	-.041	-2.412	.016	-116.688	48.227	-.041	-2.420	.016
Alcohol	45.319	17.582	.041	2.578	.010	45.125	17.599	.040	2.564	.010	45.222	17.603	.041	2.569	.010	45.247	17.605	.041	2.570	.010
Smoking	-180.721	91.543	-.033	-1.974	.048	-182.086	91.792	-.033	-1.984	.047	-181.270	91.791	-.033	-1.975	.048	-181.168	91.800	-.033	-1.974	.049
Crowding	-146.353	93.444	-.025	-1.566	.117	-147.161	93.646	-.026	-1.571	.116	-147.289	93.652	-.026	-1.573	.116	-147.018	93.664	-.026	-1.570	.117
Marital Status	-.678	41.764	.000	-.016	.987	-.498	41.829	.000	-.012	.991	-1.720	41.846	-.001	-.041	.967	-2.508	41.885	-.001	-.060	.952
Maternal Age	113.326	12.872	.146	8.804	.000	113.451	12.883	.146	8.806	.000	114.032	12.886	.147	8.849	.000	113.980	12.888	.147	8.844	.000
Antenatal Depression						2.500	13.909	.003	.180	.857	-18.589	35.760	-.026	-.520	.603	-17.782	35.806	-.025	-.497	.619
5-HTTLPR						17.805	75.766	.004	.235	.814	24.127	75.953	.005	.318	.751	24.069	75.960	.005	.317	.751
Depression x Gender											60.389	75.848	.038	.796	.426	58.592	75.954	.037	.771	.441
Depression x 5-HTTLPR											11.071	16.093	.033	.688	.492	10.673	16.118	.032	.662	.508
5-HTTLPR x Gender											18.655	11.281	.026	1.654	.098	34.013	35.019	.047	.971	.331
Depression x 5-HTTLPR x Gender																-7.471	16.126	-.022	-.463	.643
F(8,39931)=17.39 , p<.001					F(10,3989)=13.91 , p<.001					F(13,3986)=11.01 , p<.001					F(14,3985)= 10.23, p<.001					

Appendix 23: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and number nighttime awakenings at 30 months, n=4,133.

Variables	Step 1 R ² =.006					Step 2 R ² =.007					Step 3 R ² =.007					Step 4 R ² =.007				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.004	.003	.019	1.174	.240	.002	.004	.008	.429	.668	.002	.004	.008	.428	.669	.002	.004	.008	.425	.671
Gender	-.023	.015	-.023	-1.475	.140	-.023	.015	-.023	-1.475	.140	-.006	.047	-.006	-.127	.899	-.003	.047	-.003	-.055	.956
Ed. Qualification	-.048	.014	-.059	-3.457	.001	-.048	.014	-.058	-3.402	.001	-.047	.014	-.058	-3.384	.001	-.048	.014	-.058	-3.409	.001
Alcohol	.002	.005	.006	.374	.709	.002	.005	.005	.336	.737	.002	.005	.005	.331	.741	.002	.005	.005	.335	.738
Smoking	-.001	.026	-.001	-.053	.958	-.003	.027	-.002	-.124	.902	-.003	.027	-.002	-.129	.897	-.003	.027	-.002	-.130	.896
Crowding	.052	.027	.031	1.901	.057	.050	.027	.030	1.843	.065	.050	.027	.030	1.851	.064	.051	.027	.031	1.864	.062
Marital Status	-.001	.012	-.002	-.112	.911	-.001	.012	-.001	-.079	.937	-.001	.012	-.001	-.086	.931	-.002	.012	-.002	-.144	.886
Maternal Age	.005	.004	.021	1.229	.219	.005	.004	.021	1.265	.206	.005	.004	.021	1.262	.207	.005	.004	.021	1.253	.210
Antenatal Depression						.004	.004	.018	.941	.347	.001	.010	.005	.094	.925	.002	.010	.008	.154	.877
5-HTTLPR						.009	.022	.006	.404	.686	.009	.022	.006	.401	.688	.009	.022	.006	.407	.684
Depression x Gender											-.008	.022	-.018	-.373	.709	-.010	.022	-.021	-.438	.661
Depression x 5-HTTLPR											.001	.005	.015	.298	.765	.001	.005	.012	.236	.813
5-HTTLPR x Gender											.001	.003	.004	.227	.821	.014	.010	.065	1.328	.184
Depression x 5-HTTLPR x Gender																-.006	.005	-.065	-1.325	.185
	F(8,4016)=3.16 , p<.001					F(10,4014)=2.63 , p<.001					F(13,4011)=2.04 , p<.001					F(14,4010)=2.02 , p<.001				

Appendix 24: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep problems at 30 months, n=4,179

Variables	Step 1 R2=.038					Step 2 R2=.043					Step 3 R2=.044					Step 4 R2=.044				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.054	.007	.124	7.855	.000	.032	.008	.073	3.827	.000	.032	.008	.074	3.838	.000	.032	.008	.074	3.837	.000
Gender	-.090	.031	-.046	-2.916	.004	-.090	.031	-.046	-2.912	.004	-.024	.094	-.012	-.258	.796	-.029	.094	-.015	-.305	.760
Ed. Qualification	-.166	.028	-.101	-5.948	.000	-.159	.028	-.096	-5.711	.000	-.159	.028	-.096	-5.708	.000	-.159	.028	-.096	-5.694	.000
Alcohol	.006	.010	.009	.593	.553	.005	.010	.008	.510	.610	.006	.010	.009	.539	.590	.005	.010	.008	.532	.595
Smoking	.098	.053	.030	1.832	.067	.082	.053	.026	1.541	.123	.082	.053	.026	1.543	.123	.082	.053	.025	1.537	.124
Crowding	.025	.054	.007	.457	.647	.009	.054	.003	.159	.873	.010	.054	.003	.176	.860	.009	.054	.003	.167	.868
Marital Status	-.014	.024	-.010	-.593	.553	-.010	.024	-.007	-.408	.683	-.011	.024	-.007	-.435	.664	-.010	.024	-.007	-.399	.690
Maternal Age	-.021	.007	-.046	-2.745	.006	-.020	.007	-.044	-2.620	.009	-.020	.007	-.044	-2.621	.009	-.020	.007	-.043	-2.610	.009
Antenatal Depression						.037	.008	.089	4.612	.000	.053	.021	.128	2.575	.010	.052	.021	.126	2.535	.011
5-HTTLPR						-.011	.044	-.004	-.248	.804	-.015	.044	-.005	-.330	.741	-.014	.044	-.005	-.328	.743
Depression x Gender											-.032	.044	-.035	-.730	.465	-.030	.044	-.033	-.686	.493
Depression x 5-HTTLPR											-.008	.009	-.040	-.830	.407	-.007	.009	-.038	-.789	.430
5-HTTLPR x Gender											.004	.007	.009	.571	.568	-.011	.020	-.027	-.557	.578
Depression x 5-HTTLPR x Gender																.007	.009	.038	.783	.434
	F(8,3924)=19.46 , p<.001					F(10,3922)=17.77 , p<.001					F(13,919)=13.78 , p<.001					F(14,3918)=12.84 , p<.001				

Appendix 25: Unadjusted associations between sleep variables, antenatal depression and covariates.

	Sleep duration at 6 months	Awakenings at 6 months	Sleep duration at 24 months	Awakenings at 24 months	Antenatal Depression	Postnatal Depression	5-HTTLPR
Sleep duration at 6 months	_____						.021(.457)
Awakenings at 6 months	-.059(.013)	_____					.029(.301)
Sleep duration at 24 months	.132**(.000)	-.149**(.000)	_____				.079(.495)
Awakenings at 24 months	.001(.964)	.196**(.000)	-.223**(.000)	_____			-.011(.973)
Antenatal Depression	-.061(.013)	.004(.876)	-.031(.151)	.048(.024)	_____		.046(.105)
Postnatal Depression	-.035(.158)	.046(.066)	-.068(.002)	.045(.040)	.520**(.000)	_____	.044(.122)
Educational Qualification	.001(.968)	.067(.004)	-.009(.678)	-.060(.003)	-.204**(.000)	-.123**(.000)	.001(.970)
Alcohol	-.002(.924)	.034(.161)	.023(.272)	.000(.981)	-.051(.007)	-.007(.752)	-.024(.127)
Smoking	.024(.331)	-.024(.318)	.022(.315)	.025(.235)	.206**(.000)	.131**(.000)	.002(.881)
Crowding	.001(.982)	.102**(.000)	-.003(.872)	.064(.002)	.089**(.000)	-.018(.412)	-.018(.258)
Marital Status	-.046(.052)	.043(.068)	-.067**(.001)	.073**(.000)	.269**(.000)	.194**(.000)	-.021(.464)
Maternal Age	.009(.701)	.070(.003)	-.036(.081)	.009(.673)	-.211**(.000)	-.123**(.000)	-.011(.483)
**.Correlation at the .001 level							

Appendix 26: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 6 months in Generation R, n=1,317

Variables	Step 1 R ² =.005					Step 2 R ² =.009					Step 3 R ² =.009					Step 4 R ² =.010				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	-.039	.039	-.029	-1.015	.310	.002	.044	.001	.046	.964	.002	.045	.002	.046	.964	.001	.045	-.001	-.022	.983
Gender	-.011	.028	-.011	-.386	.700	-.011	.028	-.011	-.408	.683	-.009	.031	-.009	-.307	.759	-.012	.031	-.012	-.377	.706
Ed. Qualification	.009	.030	.009	.286	.775	.004	.030	.004	.141	.888	.004	.030	.004	.139	.889	.004	.030	.004	.125	.901
Alcohol	-.024	.066	-.011	-.364	.716	-.023	.066	-.010	-.348	.728	-.021	.066	-.009	-.321	.748	-.023	.066	-.010	-.345	.730
Smoking	.101	.073	.040	1.397	.163	.118	.073	.047	1.612	.107	.117	.073	.046	1.598	.110	.119	.073	.047	1.624	.105
Crowding	-.009	.036	-.007	-.248	.804	-.005	.036	-.004	-.148	.882	-.004	.036	-.003	-.123	.902	-.003	.036	-.002	-.075	.940
Marital Status	-.102	.139	-.021	-.730	.465	-.084	.139	-.017	-.603	.547	-.083	.139	-.017	-.593	.554	-.086	.139	-.018	-.614	.539
Maternal Age	-.014	.008	-.055	-1.814	.070	-.014	.008	-.056	-1.836	.067	-.014	.008	-.056	-1.836	.067	-.014	.008	-.056	-1.840	.066
Antenatal Depression						-.114	.058	-.064	-1.961	.050	-.113	.058	-.064	-1.938	.053	-.112	.058	-.063	-1.923	.055
5-HTTLPR						.025	.028	.025	.898	.370	.023	.030	.023	.760	.447	.026	.030	.026	.860	.390
Depression x Gender											-.007	.045	-.004	-.144	.886	3.198E-5	.046	.000	.001	.999
Depression x 5-HTTLPR											.017	.028	.017	.622	.534	.026	.030	.026	.860	.390
5-HTTLPR x Gender											.007	.049	.004	.132	.895	.003	.050	.002	.066	.947
Depression x 5-HTTLPR x Gender																.034	.046	.023	.743	.458
	F(8,1309)=1 , p=.429					F(10,1306)=1.17 , p=.308					F(13,1303)=.93 , p=.52					F(14,1302)=.90 , p=.55				

Appendix 27: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and awakenings at 6 months in Generation R, n=1,283

Variables	Step 1 R ² =.038					Step 2 R ² =.043					Step 3 R ² =.044					Step 4 R ² =.044				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.033	.025	.037	1.300	.194	.048	.029	.053	1.628	.104	.052	.030	.058	1.763	.078	.057	.030	.063	1.897	.058
Gender	.050	.020	.078	2.518	.012	.049	.020	.076	2.450	.014	.048	.020	.075	2.421	.016	.049	.020	.076	2.458	.014
Ed. Qualification	.030	.043	.020	.692	.489	.030	.044	.020	.684	.494	.028	.044	.019	.634	.526	.030	.044	.020	.680	.497
Alcohol	-.062	.048	-.037	-1.300	.194	-.057	.048	-.034	-1.183	.237	-.056	.048	-.034	-1.155	.248	-.058	.048	-.035	-1.199	.231
Smoking	.084	.024	.100	3.541	.000	.085	.024	.101	3.575	.000	.085	.024	.100	3.542	.000	.083	.024	.098	3.449	.001
Crowding	.225	.090	.071	2.485	.013	.229	.091	.073	2.521	.012	.225	.091	.072	2.479	.013	.228	.091	.072	2.513	.012
Marital Status	.005	.005	.032	1.068	.286	.005	.005	.031	1.030	.303	.005	.005	.031	1.023	.306	.005	.005	.031	1.030	.303
Maternal Age	-.072	.018	-.108	-3.905	.000	-.072	.018	-.108	-3.904	.000	-.065	.020	-.097	-3.161	.002	-.062	.021	-.092	-3.010	.003
Antenatal Depression						-.039	.038	-.033	-1.008	.314	-.041	.039	-.035	-1.065	.287	-.042	.039	-.036	-1.091	.275
5-HTTLPR						.000	.018	.000	-.013	.990	.003	.020	.005	.156	.876	-.001	.020	-.001	-.044	.965
Depression x Gender											.014	.030	.014	.457	.648	.005	.031	.005	.178	.859
Depression x 5-HTTLPR											-.016	.018	-.024	-.867	.386	-.028	.020	-.042	-1.388	.165
5-HTTLPR x Gender											.028	.033	.027	.865	.387	.032	.033	.030	.988	.323
Depression x 5-HTTLPR x Gender																-.046	.031	-.046	-1.517	.130
	F(8,1275)=6.05 , p<.001					F(10,1273)=4.94 , p<.001					F(13,1270)=1.71 , p<.001					F(14,1269)=3.8 , p<.001				

Appendix 28: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 24 months in Generation R, n=1,626

Variables	Step 1 R ² =.016					Step 1 R ² =.017					Step 1 R ² =.018					Step 1 R ² =.020				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	-.071	.029	-.061	-2.429	.015	-.082	.034	-.071	-2.404	.016	-.081	.035	-.070	-2.338	.020	-.080	.035	-.069	-2.322	.020
Gender	-.027	.022	-.033	-1.196	.232	-.027	.022	-.033	-1.201	.230	-.027	.022	-.033	-1.193	.233	-.027	.022	-.034	-1.206	.228
Ed. Qualification	.070	.048	.038	1.447	.148	.071	.049	.039	1.472	.141	.069	.049	.038	1.418	.156	.068	.049	.037	1.392	.164
Alcohol	.048	.053	.023	.912	.362	.045	.053	.022	.853	.394	.047	.053	.023	.879	.380	.049	.053	.024	.926	.355
Smoking	.011	.027	.011	.415	.678	.011	.027	.011	.427	.670	.011	.027	.010	.404	.686	.014	.027	.013	.529	.597
Crowding	-.165	.104	-.041	-1.589	.112	-.167	.105	-.041	-1.595	.111	-.172	.105	-.043	-1.644	.100	-.177	.105	-.044	-1.686	.092
Marital Status	-.007	.006	-.034	-1.251	.211	-.007	.006	-.033	-1.190	.234	-.007	.006	-.032	-1.172	.241	-.007	.006	-.033	-1.206	.228
Maternal Age	.071	.020	.086	3.480	.001	.071	.020	.086	3.494	.000	.082	.023	.099	3.571	.000	.079	.023	.095	3.433	.001
Antenatal Depression						.025	.045	.017	.561	.575	.023	.046	.015	.505	.613	.021	.046	.014	.454	.650
5-HTTLPR						.021	.020	.025	1.008	.314	.020	.022	.025	.900	.368	.022	.022	.027	.971	.332
Depression x Gender											-.001	.037	-.001	-.035	.972	.001	.037	.001	.025	.980
Depression x 5-HTTLPR											-.017	.020	-.021	-.852	.394	-.001	.022	-.001	-.035	.972
5-HTTLPR x Gender											.039	.038	.029	1.024	.306	.036	.038	.027	.960	.337
Depression x 5-HTTLPR x Gender																.064	.036	.048	1.762	.078
	F(8,1617)=3.31 , p=.001					F(10,1615)=2.78 , p=.002					F(13,1612)=2.27 , p=.006					F(14,1611)=2.33 , p=.003				

Appendix 29: Hierarchical Regression Analysis testing the moderating effect of 5-HTTLPR and gender on antenatal depression and sleep duration at 24 months in Generation R, n=1,677

Variables	Step 1 R ² =.017					Step 2 R ² =.018					Step 3 R ² =.019					Step 4 R ² =.022				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Postnatal Depression	.035	.022	.041	1.642	.101	.027	.025	.031	1.055	.291	.024	.025	.028	.956	.339	.023	.025	.027	.915	.360
Gender	-.003	.015	-.004	-.169	.866	-.003	.015	-.004	-.173	.863	.004	.017	.006	.215	.830	.007	.017	.012	.432	.666
Ed. Qualification	-.030	.017	-.049	-1.800	.072	-.030	.017	-.049	-1.774	.076	-.029	.017	-.048	-1.755	.079	-.029	.017	-.047	-1.707	.088
Alcohol	.037	.036	.027	1.029	.303	.037	.036	.027	1.022	.307	.036	.036	.026	.985	.325	.037	.036	.026	1.006	.314
Smoking	.037	.040	.024	.938	.348	.035	.040	.022	.873	.383	.037	.040	.024	.924	.356	.035	.040	.023	.885	.377
Crowding	.065	.020	.080	3.214	.001	.065	.020	.080	3.194	.001	.066	.020	.081	3.247	.001	.063	.020	.078	3.122	.002
Marital Status	.172	.076	.057	2.271	.023	.163	.076	.054	2.139	.033	.157	.076	.052	2.054	.040	.159	.076	.053	2.087	.037
Maternal Age	-.003	.004	-.021	-.765	.445	-.003	.004	-.020	-.757	.449	-.003	.004	-.020	-.740	.460	-.003	.004	-.019	-.695	.487
Antenatal Depression						.025	.033	.022	.764	.445	.031	.034	.027	.916	.360	.031	.034	.027	.911	.362
5-HTTLPR						-.014	.015	-.022	-.886	.376	-.022	.017	-.035	-1.307	.191	-.025	.017	-.039	-1.484	.138
Depression x Gender											-.033	.026	-.033	-1.236	.217	-.039	.027	-.040	-1.473	.141
Depression x 5-HTTLPR											.002	.015	.003	.118	.906	-.012	.017	-.019	-.711	.477
5-HTTLPR x Gender											.024	.028	.023	.849	.396	.029	.028	.028	1.036	.300
Depression x 5-HTTLPR x Gender																-.055	.026	-.055	-2.075	.038
	F(8,1668)=3.6 , p<.001					F(10,1666)=3 , p=.001					F(13,1663)=2.45 , p=.002					F(14,1662)=2.63 , p=.001				

APPENDICES FOR CHAPTER 4

Appendix 30: The Edinburgh Postnatal Depression Scale (EPDS)

The way you are feeling in yourself is very important in understanding your experience of caring for a young child. These questions are about how you have been feeling in the <u>past 7 days</u>, not just how you feel today. Each statement about the way you feel has four different choices. Please tick the circle next to the answer that comes closest to the way you have been feeling over the past week.	
1	I have been able to laugh and see the funny side of things... ☐ As much as I always could ☐ Not quite as much now ☐ Definitely not so much now ☐ Not at all
2	I have looked forward with enjoyment to things... ☐ As much as I ever did ☐ Rather less than I used to ☐ Definitely less than I used to ☐ Hardly at all
3	I have blamed myself unnecessarily when things went wrong... ☐ Yes, most of the time ☐ Yes, some of the time ☐ Not very often ☐ No, never
4	I have been anxious or worried for no good reason... ☐ Not, not at all ☐ Hardly ever ☐ Yes, sometimes ☐ Yes, very often
5	I have felt scared or panicky for no very good reason... ☐ Yes, quite a lot ☐ Yes, sometimes ☐ No, not much ☐ No, not at all
6	Things have been getting on top of me... ☐ Yes, most of the time I haven't been able to cope at all ☐ Yes, sometimes I haven't been coping as well as usual ☐ No, most of the time I have coped quite well ☐ No, I have been coping as well as ever
7	I have been so unhappy that I have had difficulty sleeping... ☐ Yes, most of the time ☐ Yes, sometimes ☐ Not very often ☐ No, not at all
8	I have felt sad or miserable... ☐ Yes, most of the time ☐ Yes, quite often ☐ Not very often ☐ No, not at all
9	I have been so unhappy that I have been crying... ☐ Yes, most of the time ☐ Yes, quite often ☐ Only occasionally ☐ No, never
10	The thought of harming myself has occurred to me... ☐ Yes, quite often ☐ Sometimes ☐ Hardly ever ☐ Never

Appendix 31: Questionnaire on demographics characteristics of participants

A. About you

1. What is your first language?
2. What is the main language you will use with the baby?.....
3. How would you describe your ethnic background?

White ☐ British ☐ Irish ☐ Any other background please specify 	Black or Black British ☐ Caribbean ☐ African ☐ Any other Black background please specify 	Chinese ☐ Chinese
Mixed ☐ White and Black Caribbean ☐ White and Black African ☐ White and Asian ☐ Any other mixed background please specify 	Asian or Asian British ☐ Indian ☐ Pakistani ☐ Bangladeshi ☐ Any other Asian background please specify 	Other ethnic group ☐ Any other please specify ☐ Decline to specify

4. Which of the following best describes your current situation?

☐ Single
 ☐ Married
 ☐ Living Together
 ☐ Stable relationship (lot living together)

☐ Other (please specify).....

5. Which of the following best describes your current employment:

☐ Full-Time
 ☐ Part-time
 ☐ No job
 ☐ Studying/Training
 ☐ Maternity leave

☐ Self-employed
 ☐ Long term sick leave
 ☐ Other (please specify).....

6. Your current/last job title:.....

7. If not currently employed, what was the date of leaving your last job?.....

8. To date, which qualifications do you hold? (please indicate highest qualification)?

☐ GCSEs/O-Level
 ☐ A-Level
 ☐ Undergraduate degree
 ☐ NVQ
 ☐ Post-graduate degree
 ☐ Other (please specify).....

9. What is your yearly household income (before tax):

☐ under £7,999
 ☐ £8,000-14,999
 ☐ 15,000-24,999
 ☐ £25,000-39,999

☐ £40,000-69,999 ☐ above £70,000

B. THIS PREGNANCY

Was this pregnancy planned? ☐ Yes ☐ No

If no, an unplanned pregnancy can be experienced in different ways.

How did you feel about it? ☐ I was pleased about the pregnancy virtually from the start

☐ I had mixed feelings initially, but am now pleased about it

☐ I still have mixed feelings

☐ I am mostly not happy about the pregnancy

Due date: (DD/MM/YYYY).....

How many weeks pregnant are you? weeks and days

Are you currently on any medication? If so please specify (with the drug name if possible)

.....

During this pregnancy have you had any complications (such as pregnancy diabetes, preeclampsia, high blood pressure)?

☐ No ☐ Yes please specify

C. YOUR HABITS

We are interested in any changes to your lifestyle that you have made since learning you are pregnant.

Smoking

Have you smoked at all since conceiving your child?

☐ No ☐ Yes

If so, then when did you last smoke a cigarette?.....

Since learning you were pregnant, how many cigarettes did you smoke on average per week?

☐ none ☐ 1-5 ☐ 6-10 ☐ 11-15 ☐ 16-20

☐ 21-25 ☐ 26-30 ☐ 30+

Drinking Alcohol

Have you drunk alcohol at all since conceiving your child?

☐ No ☐ Yes

If so, then when did you last drink?

Since learning you were pregnant, how many units of alcohol have you drunk on average per week?

☐ none ☐ 1-5 ☐ 6-10 ☐ 11-15 ☐ 16-20

☐ 21-25

1 unit = 1 glass of wine
½ pint of beer or lager
1 pub measure of spirit

D. YOUR HEALTH

Do you have any medical or health problems? _____

Are you currently on any medication? No Yes

Have you ever been on long-term medication for a physical problem, or an emotional one, or for anything else, like sleeping problems? (If yes, please describe) No
Yes

Are you currently undergoing any treatment or counselling or awaiting treatment or counselling?

No Yes

Have you ever had a period in which you were anxious or worried? No Yes Don't know

(for at least 2 weeks)

If yes, did you have this in the past year? No Yes

Have you been treated for this by a family doctor or psychologist? No Yes

Have you ever had a period in which you felt very down or depressed? No Yes Don't know

(for at least 2 weeks)

If yes, did you have this in the past year? No Yes

Have you been treated for this by a family doctor or psychologist? No Yes

Notes:

Appendix 32: Pittsburgh Sleep Quality Index

The following questions relate to your usual sleep habits during the ***past month only***. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month, when have you usually gone to bed at night?

USUAL BED TIME _____

During the past month, how long (in minutes) has it usually take you to fall asleep each night?

NUMBER OF MINUTES _____

During the past month, when have you usually gotten up in the morning?

USUAL GETTING UP TIME _____

During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

During the past month, how often have you had trouble sleeping because you...				
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
Cannot get to sleep within 30 minutes				
Wake up in the middle of the night or early morning				
Have to get up to use the bathroom				
Cannot breathe comfortably				
Cough or snore loudly				
Feel too cold				
Feel too hot				
Had bad dreams				
Have pain				
Other reason(s), (please include external factors if relevant e.g. living on a main road or close to an airport) please describe				

How often during the past month have you had trouble sleeping because of this?				

During the past month, how would you rate your sleep quality overall?

Very good _____ Fairly good _____

Fairly Bad _____ Very bad _____

During the past month, how often have you taken medicine (prescribed or over the counter) to help you sleep?

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

During the past month, have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____ Only a very slight problem _____

Somewhat of a problem _____ A very big problem _____

Do you have a bed partner or roommate?

No bed partner or roommate _____ Partner / roommate in other room _____

Partner in the same room, but not same bed _____ Partner in same bed _____

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
Loud snoring				
Long pauses between breathes while asleep				
Legs twitching or jerking while you sleep				
Episodes of disorientation or confusion during sleep				
Other restlessness while you sleep, please describe _____				

Appendix 33: The State Trait Anxiety inventory

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel right now, that is, at this moment in time. There are no right and wrong answers. Do not spend too much time on each statement but give the answer which seems to describe your present feeling best.

	Not at all	Somewhat	Moderately	Very much
I feel calm	1	2	3	4
I feel secure	1	2	3	4
I am tense	1	2	3	4
I feel strained	1	2	3	4
I feel at ease	1	2	3	4
I feel upset	1	2	3	4
I am presently worrying over possible misfortunes	1	2	3	4
I feel satisfied	1	2	3	4
I feel frightened	1	2	3	4
I feel comfortable	1	2	3	4
I feel self confident	1	2	3	4
I feel nervous	1	2	3	4
I am jittery	1	2	3	4
I feel indecisive	1	2	3	4
I am relaxed	1	2	3	4
I feel content	1	2	3	4
I am worried	1	2	3	4
I feel confused	1	2	3	4
I feel steady	1	2	3	4
I feel pleasant	1	2	3	4

Appendix 34: Stressful Life Events Questionnaire

Listed below are a number of events that may have brought changes in your life. Have any of these events occurred to you since you became pregnant with this baby? If so, please assess how much effect it had on you. If one of these events occurred more than once, please rate the effect on you of the most serious. Many of the events listed are of personal nature. Your answers will be held in strict confidence.				
	Life Event:	No, this has never happened	Yes this has happened, and it affected me a little	Yes this has happened, and it affected me a lot
1	You were admitted to the hospital			
2	You had a serious accident or illness			
3	Your partner had a serious accident or illness			
4	A friend or family member had a serious accident or illness			
5	You were in trouble with the law			
6	Your partner was in trouble with the law			
7	You were separated / divorced			
8	Your partner lost his job			
9	You experienced a significant drop in income			
10	You had a major financial problem			
11	Your car or house was burgled			
12	You became homeless			
13	You found that your partner did not want your child			
14	You had a serious argument with your partner			
15	You had a serious argument with your family or friends			
16	Your partner was physically cruel to you			
17	Your partner was emotionally cruel to you			
18	You were physically cruel to your partner			
19	You attempted suicide			
20	A friend or relative attempted suicide			
21	You suffered from mental illness			
22	A friend or relative suffered from mental illness			
23	Your partner died			
24	A friend or relative died			
25	You had an extramarital sexual affair			
26	Your partner had an extramarital sexual affair			

Appendix 35: The Brief Sleep Quality Index

Please mark only one (most appropriate) choice, when you respond to items with a few options.

1. Sleeping arrangement:
☐ Infant crib in a separate room ☐ Infant crib in parents' room
☐ In parents' bed ☐ Infant crib in room with sibling
☐ Other, Specify: _____
2. In what position does your child sleep most of the time?
☐ On his/her belly ☐ On his/her side ☐ On his/her back
3. How much time does your child spend in sleep during the NIGHT (between 7 in the evening and 7 in the morning)? Hours: _____ Minutes: _____
4. How much time does your child spend in sleep during the DAY (between 7 in the morning and 7 in the evening)? Hours: _____ Minutes: _____
5. Average number of night wakings per night: _____
6. How much time during the night does your child spend in wakefulness (from 10 in the evening to 6 in the morning)? Hours: _____ Minutes: _____
7. How long does it take to put your baby to sleep in the evening?
Hours: _____ Minutes: _____
8. How does your baby fall asleep?
☐ While feeding ☐ Being rocked
☐ Being held ☐ In bed alone
☐ In bed near parent
9. When does your baby usually fall asleep for the night: Hours: _____ Minutes: _____
10. Do you consider your child's sleep as a problem?
☐ A very serious problem ☐ A small problem ☐ Not a problem at all

Appendix 36: Maternal cognitions about infant sleep questionnaire

Here are a series of statements about thoughts and feelings mothers may have when faced with a child that won't sleep. After reading each statement circle the response that most closely represents how you yourself would feel with baby. Don't take too long thinking about your answer and don't hesitate to use the extreme responses if appropriate.

	Strongly agree	Moderately agree	Mildly agree	Mildly disagree	Moderately disagree	Strongly disagree
1. When my child cries at night, I think something awful might have happened to him/her						
2. When my child wakes at night, I think I might not have fed him/her enough during the day						
3. My child might die unexpectedly in his/her sleep						
4. My child will feel abandoned if I don't respond immediately to his/her cries at night						
5. My child might go hungry if I don't give him/her a feed at night						
6. It is all right to allow my child to cry at night						
7. When my child cries at night, I think I might lose control and harm him/her						
8. When my child wakes at night, I think I might not have given him/her enough attention during the day						
9. I should be getting up during the night to check that my child is all right						
10. If I try to resist my child's demands at night, then I think I might get very angry						
11. When my child wakes crying, I always know what he/she needs						
12. When my child cries at night and needs me, I wish he/she wasn't so demanding						
13. If I try to resist my child's demands at night, then he/she will get even more upset						
14. When my child doesn't sleep at night, I doubt my competence as a parent						
15. If I say no to my child's demands at night, then that means I'm a bad mother						
16. I am able to let my child sleep on his/her own						
17. When my child cries at night, I can find myself thinking I wish I had never had a child						
18. I should respond straightaway when my child wakes crying at night						
19. I am able to resist my child's demands when he/she wakes at night						
20. If I give up feeding at night, then he/she will never sleep						

Actigraphy Instructions

Important details for the use of the ACTIWATCH

- Wear the ACTIWATCH on your non-dominant wrist:
- Right handers wear it on their left wrist; Left handers wear it on their right wrist.
- Wear the ACTIWATCH continuously day and night around.
- Take the ACTIWATCH off when having a bath or a shower.
- Don't forget to put it on again.
- Indoors: Don't cover the ACTIWATCH with your sleeve.
- Outdoors: Don't cover the ACTIWATCH with your sleeves, except when it will get very wet.
- Be careful and prevent it from heavy wetness and any damage!

Completion of the diary

IMPORTANT TO NOTE:

- When was the ACTIWATCH taken off?
- For what reason (e.g. shower)
- When was ACTIWATCH put on again?
- Indicate Bedtime / Lights off
- Indicate Get-up time / Lights on
- Indicate when Awake in bed
- Indicate Naps
- Indicate calm activities such as reading, computer games, watching TV
- Indicate Sports e.g. jogging
- Indicate when unwell or sick
- Indicate time of medication intake

Sample of daily activities diary when completed

DETAILED 2-DAY DIARY ACCOMPANYING ACTIVITY MONITORING

Code: _____ Date: _____ day 1 Page: EXAMPLE

Please remark: Get-up time, Bedtime, Activatch on/off, Have a shower, Lights on/off, Awake in bed, Medication, Naps, Go out (to see friends, take a walk), Reading, Watching TV, Meals.

TIME	REMARKS	TIME	REMARKS	TIME	REMARKS
12 00 AM	Watching TV	08 00 AM	Shower	4 00 PM	Drive home shopping
30	shower	30	breakfast	30	
01 00 AM	Curtains closed	09 00 AM	drive to work by car	5 00 PM	nap
30	Lights off	30	at work in the office	30	
02 00 AM	asleep	10 00 AM	work on computer	6 00 PM	household
30		30		30	
03 00 AM		11 00 AM		7 00 PM	Went out by train
30		30		30	
04 00 AM		12 00 PM	Neon	8 00 PM	took medication
30		30	Lunch time	30	
05 00 AM	Been lying in bed	1 00 PM		9 00 PM	Dinner in Restaurant with Friends
30	Unable to sleep	30	back to work on computer	30	
06 00 AM	asleep	2 00 PM		10 00 PM	
30		30	Feeling drained	30	
07 00 AM	Alarm clock	3 00 PM		11 00 PM	snack
30	Open curtains	30		30	Feeling bored
	Feeling drowsy			30	shower
				30	Close curtains
					Lights off

DETAILED 2-DAY DIARY ACCOMPANYING ACTIVITY MONITORING

Code: _____ Date: _____ day 2 Page: EXAMPLE

Please remark: Get-up time, Bedtime, Activatch on/off, Have a shower, Lights on/off, Awake in bed, Medication, Naps, Go out (to see friends, take a walk), Reading, Watching TV, Meals.

TIME	REMARKS	TIME	REMARKS	TIME	REMARKS
12 00 AM		08 00 AM	Curtains open	4 00 PM	nap
30		30	Shower	30	Wake up by phone
01 00 AM	Went to bed	09 00 AM	breakfast	5 00 PM	household
30	Lights off	30	drive to work by car	30	clearing
02 00 AM	Awake in bed	10 00 AM	at work in the office	30	ironing, while watching TV
30	unable to sleep, so made a cup of tea	11 00 AM	Work on computer	6 00 PM	
03 00 AM		12 00 PM	Noon Lunch time	30	
30		30		7 00 PM	
04 00 AM	asleep	1 00 PM	shopping	30	look medication
30		30	back to work work on computer	30	Cooking food
05 00 AM		2 00 PM		8 00 PM	Activatch briefly
30		30		30	Taken off and put on again
06 00 AM		3 00 PM	drive home	9 00 PM	supper
30	Alarm clock	30		30	talking with sister
	Feeling tired			30	
	Awake in bed			30	Curtains closed
				30	snack
				30	Shower
				30	In bed, reading
					Lights off

Appendix 38: Instructions for saliva collection for mother and child

Subject ID: _____

Date: _____

Instructions for collecting Saliva Samples

Please use **tube 1** as soon as you wake up (while lying in bed). For example 7:30 am

Use **tube 2**: 15 minutes later, while still lying in bed, for example 7:45 am

Use **tube 3**: 15 minutes after tube 2, for example 8:00 am

Use **tube 4**: 15 minutes after tube 3, for example 8:15 am

To collect samples, please open the tube and deposit as much saliva as possible. Please try to remain in the same position (e.g. lying in bed) for the entire collection period. Please store in the refrigerator or a cool place until you come to your study visit. Please remember **not to have anything to eat or drink** and **not to brush teeth** prior to sampling. Please **do not smoke** prior to sampling and **do not have alcohol** the night before.

With regard to the morning that you provide samples, could you tell us:

What time you went to sleep the night before: _____

What time you woke up: _____

Did you wake up at night: Yes / No

If yes, approximate number of times and duration: _____

Did you use an alarm/radio clock to wake you up this morning: Yes / No

Please indicate the day of your cycle on which you took the saliva sample (e.g. day 2 of a 28 day cycle: 2/28): _____

Sample Times: _____ Date: _____

Tube 1: _____ Pack no: 1/2

Tube 2: _____

Tube 3: _____

Tube 4: _____

PLEASE CONTACT Elena Netsi ONCE YOU HAVE COMPLETED THE COLLECTION

Instructions for collecting Saliva Samples for Baby

Please use **tube 1** as soon as he/she wakes up (while lying in bed). For example 7:30 am

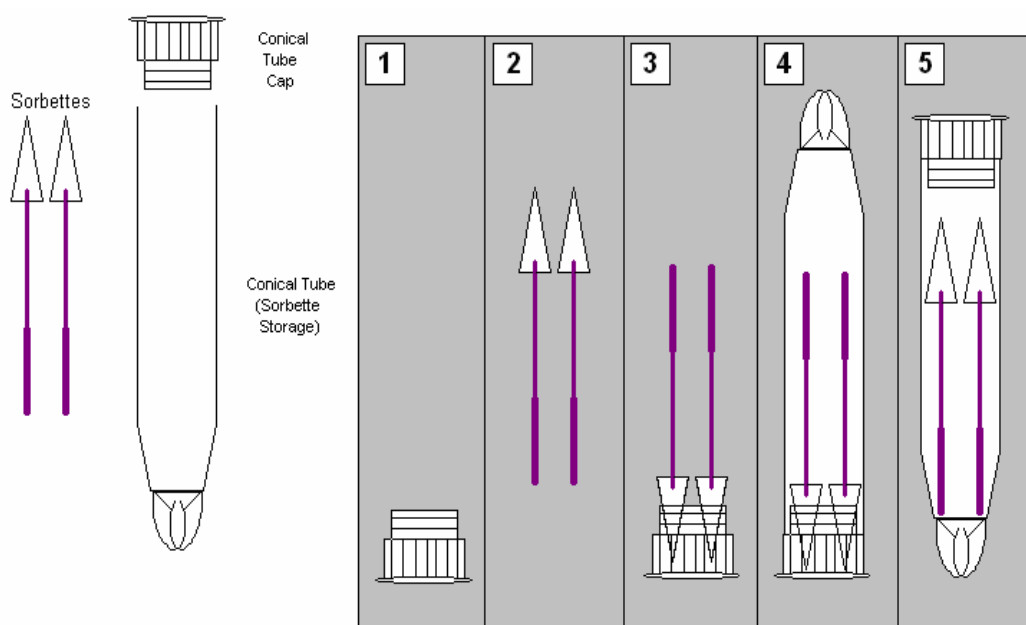
Use **tube 2**: 15 minutes later, while he/she is still lying in bed, for example 7:45 am

Use **tube 3**: 15 minutes after tube 2, for example 8:00 am

Use **tube 4**: 15 minutes after tube 3, for example 8:15 am

1. To collect samples, remove two sorbettes from envelope. Close envelope to protect the remaining sorbettes from contact with moisture.
2. Put sorbettes **under the tongue** for 15 to 30 seconds at a time and re-introduced as needed until the sorbette is saturated (at least 60-90 seconds total time). **Do not** stop collecting when the sorbette begins to puff up. We generally recommend that the sorbette not be moved around in the mouth.)
3. Place Sorbettes into the conical tube cap as seen in the attached diagram. The tips should face the cap end of the tube
4. It is crucial that the saliva collected via sorbette not evaporate. Make sure the vial cap is snug and sample is frozen **within two hours** after collection.

SORBETTE SAMPLE PREPARATION



1. Place cap on a flat surface as shown.
2. Saturate two sorbettes.
3. Insert Sorbettes **tip down** into cap.
4. Slide conical storage tube over purple sticks and snap down securely onto cap.

With regard to the morning that you provide samples, could you tell us:

What time he/she went to sleep the night before: _____

What time he/she woke up: _____

Did he/she wake up at night: Yes / No

If yes, approximate number of times and duration: _____

Sample Times:

Date: _____

Tube 1: _____

Tube 2: _____

Tube 3: _____

Tube 4: _____

Appendix 39: History of depression questions asked as Part of the Clinical Interview.

PAST DEPRESSIVE EPISODE

Has there ever been another time when you were depressed or down most of the day nearly everyday, for at least 2 weeks, and when you had several of the symptoms that you described such as (mention current symptoms)? Can you tell me a bit about that?

0 = No [i.e. no past depressive episodes, go to screener]

1 = Yes

If other episodes (i.e. A21 coded 1),

How many separate times in your life have you been depressed (own words) like this?

(Check: estimate total number of discreet episodes but there is no need to inquire about each symptom in detail.)

0 = No other episodes

1 = 1 other episode

2 = 2 or more other episodes

If other episodes,

How old were you when you had the <u>first</u> episode of depression? (Record in years)
--

If other episodes,

Were you ever placed on medication for these episodes? Did you have any therapy, treatment or counselling?

0 = No

1 = Yes (specify on History sheet)

Appendix 40: Unadjusted bivariate associations between infant sleep variables assessed through actigraphy, n=14

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Actigraphy																
1. Time in Bed	—	.01 (.987)	.52 (.367)	-.14 (.818)	.01 (.993)	.14 (.824)	.28 (.644)	-.16 (.803)	.82 (.092)	.34 (.570)	.84 (.077)	.02 (.979)	-.03 (.966)	-.58 (.304)	.85* (.012)	.22(.718)
2. Assumed sleep during the night		—	.15 (.807)	.18 (.768)	.43 (.468)	.55 (.341)	-.17 (.784)	-.79** (.002)	-.11 (.866)	-.32 (.602)	-.44 (.454)	-.12 (.851)	.03 (.961)	.57 (.319)	.14 (.822)	.11 (.856)
3. Actual Sleep time during the night			—	.76 (.135)	.39 (.520)	.79 (.109)	-.67 (.221)	-.16 (.795)	.87(.056)	.87 (.058)	.52 (.373)	-.80 (.108)	-.82 (.090)	-.36 (.554)	.59 (.287)	.49* (.042)
4. Actual sleep % during the night				—	.31 (.586)	.77 (.128)	-.78** (.001)	-.08 (.896)	.367 (.545)	.71 (.179)	-.001 (.999)	-.67** (.006)	-.76* (.012)	.11 (.862)	-.05 (.930)	.51* (.034)
5. Actual sleep time over the day					—	.79 (.113)	-.34 (.572)	-.42 (.478)	.29 (.638)	.31 (.616)	-.33 (.586)	-.14 (.829)	-.14 (.825)	-.27 (.660)	.30 (.613)	.11 (.861)
6. Actual sleep time over the 24-hour period						—	-.74 (.157)	-.51 (.380)	.52 (.373)	.58 (.305)	-.08 (.900)	-.70 (.217)	-.64 (.248)	-.07 (.910)	.36 (.552)	.67 (.216)
7. Awake time during the night							—	.05 (.934)	-.25 (.692)	-.65 (.236)	.13 (.840)	.84* (.019)	.62* (.028)	-.17 (.786)	.18 (.768)	-.44 (.075)
8. Sleep latency								—	.02 (.972)	.33 (.594)	.337 (.579)	.03 (.960)	-.11 (.863)	-.47 (.426)	-.27 (.652)	-.06 (.918)
9. Immobile minutes									—	.81(.093)	.791 (.111)	-.43 (.466)	-.51 (.379)	-.71 (.176)	.45 (.065)	.61 (.274)
10. Immobile minutes %										—	.551 (.336)	-.73 (.164)	-.52 (.087)	-.60 (.281)	.40 (.498)	.78 (.118)
11. Wake bouts											—	-.18 (.772)	-.27 (.660)	-.64 (.249)	.69 (.197)	.38 (.526)
12. Mean Wake Bouts												—	.78** (.002)	-.11 (.865)	-.01 (.993)	-.67** (.006)
13. Fragmentation Index													—	.05(.942)	-.05 (.940)	-.56** (.008)
14. IS														—	-.64 (.247)	-.023 (.971)
15. IV															—	.223 (.715)
16. Relative Amplitude																—

* $p < .05$, ** $p < .01$

Appendix 41: Unadjusted bivariate associations between infant sleep variables assessed through maternal report, n=16

	1	2	3	4	5	6	7
Infant Sleep (Questionnaire)							
1. Sleep time during the night	_____	-.51(.300)	.76(.046)	-.11(.820)	.46(.302)	.06(.904)	-.48(.302)
2. Sleep time during the day		_____	.69(.09)	-.08(.870)	.57(.022)	.23(.619)	-.05(.92)
3. Sleep time during the 24-hour period			_____	-.36(.427)	.31(.504)	.47(.283)	-.58(.172)
4. Nighttime Awakenings				_____	.24(.605)	.55(.202)	.42(.353)
5. Wakefulness during the night					_____	.37(.420)	.23(.615)
6. How long does it take to put your baby to bed						_____	.30(.507)
7. When does baby usually go to sleep							_____

**p<.05, **p<.01*

Appendix 42: Unadjusted bivariate associations between maternal cognitions about sleep and infant sleep

	Limit Setting	Anger	Doubt	Feeding	Safety	Total
Infant Sleep (actigraphy)						
Sleep time	-.10(.871)	-.19(.755)	.20(.745)	-.27(.664)	.06(.930)	-.06(.918)
during the night						
Sleep time	-.27(.661)	-.11(.860)	.29(.633)	-.46(.061)	-.01(.990)	-.23(.711)
during the day						
sleep time during 24-	-.46(.441)	-.45(.445)	.06(.919)	-.78(.123)	-.21(.730)	-.47(.429)
hours						
Wake time	.19(.762)	.32(.605)	.60(.289)	.05(.931)	.51(.375)	.43(.469)
Sleep Latency	.56*(.011)	.25(.681)	-.19(.762)	.42(.479)	-.01(.989)	.50(.391)
Immobile Minutes	.18(.770)	.81(.097)	.55(.339)	.62(.270)	.70(.188)	.65(.231)
IS	-.69(.196)	-.70(.186)	-.69(.200)	-.16(.800)	-.67(.219)	-.84(.101)
IV	-.04(.953)	.59(.298)	.59*(.042)	.15(.809)	.81(.096)	.55(.341)
Relative Amplitude	-.14(.821)	-.52(.366)	-.23(.709)	-.22(.727)	-.31(.607)	-.33(.585)
Infant Sleep (maternal report)						
Sleep Duration -	-.76(.046)	-.03(.950)	.46(.299)	-.38 (.396)	.24(.609)	-.16(.736)
Night						
Sleep Duration - day	.01(.976)	.27(.552)	.24(.613)	-.49(.267)	-.21(.645)	.01(.984)
Sleep Duration - 24	-.47(.283)	.06(.905)	.44(.324)	-.45(.310)	.13(.784)	-.12(.791)
Night wakings	.69(.086)	.67(.100)	.78*(.037)	.35(.444)	.41(.356)	.69*(.011)
Wakefulness during	.37(.414)	.62(.138)	.396(.379)	-.20(.663)	-.13(.776)	.37(.412)
the night						
How long to put to	.03(.942)	.74(.058)	.59** (.006)	.43(.338)	.15(.782)	.69(.086)
bed						
When does baby	.16(.733)	.11(.816)	.35(.441)	.27(.557)	-.27(.564)	.23(.628)
usually fall asleep						

* $p < .05$, ** $p < .01$

APPENDICES FOR CHAPTER 5

Appendix 43: Descriptives of CIS-R score

	N	Range	Mean	SD
CIS-R Baseline score	36	11-43	28.92	7.64
CIS-R 15 weeks post randomization score	29	0-40	16.83	11.11
CIS-R 33 weeks post randomization score	27	0-39	14.93	11.79
CIS-R change from baseline to post-assessment score	29	(-6)-30	12.31	8.56

Appendix 44: Unadjusted associations between CIS-R change during pregnancy, infant temperament and sleep (2-tailed).

	EPDS Change score	Infant Temperament	Sleeping During the Night	Awakenings over the night	Sleep during the 24 hour period	Sleep during the day
Change in CIS-R scores	.81(.000)	-.13(.532)	-.30(.139)	.12(.575)	-.002(.991)	.118(.575)

** . Correlation is significant at the 0.01 level (2-tailed).

Appendix 45: The Infant Characteristics Questionnaire – fussy/difficult factor.

On the following questions please circle the number that is most typical of your baby. The option ‘about average’ means how you think the typical baby would be scored.

1. How easy or difficult is it for you to calm or soothe your baby when s/he is upset?						
1	2	3	4	5	6	7
Very easy			about average			difficult
2. How many times per day, on average, does your baby get fussy and irritable- for either short or long periods of time?						
1	2	3	4	5	6	7
Never	1-2 times per day	3-4 times per day	5-6 times per day	7-9 times per day	10-14 times per day	more than 15 per day
3. How easy or difficult is it for you to predict when your baby will go to sleep and wake up?						
1	2	3	4	5	6	7
Very easy			about average			difficult
4. How easily does your infant get upset?						
1	2	3	4	5	6	7
very hard to upset			about average			very easily upset
5. When your baby gets upset, how vigorously or loudly does he/she cry and fuss?						
1	2	3	4	5	6	7
very mild intensity or loudness			moderate intensity or loudness			very loud or intense
6. How does your baby react when you are dressing him/her?						
1	2	3	4	5	6	7
very well likes it			about average doesn't mind			doesn't like it at all
7. What kind of mood is your baby generally in?						
1	2	3	4	5	6	7
very happy and cheerful			neither serious no cheerful			serious
8. How changeable is your baby's mood?						
1	2	3	4	5	6	7
changes seldom and changes slowly			about average			changes often and rapidly
9. Please rate the overall degree of difficulty your baby would present for the average parent?						
1	2	3	4	5	6	7
super easy			ordinary some			highly

References

- Abeyseena, Jayawardana, & De A Seneviratne. (2009). Maternal sleep deprivation is a risk factor for small for gestational age: A cohort study. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 49(4), 382-387.
- Aiken, West, & Reno. (1991). *Multiple regression: Testing and interpreting interactions*: Sage Publications, Inc.
- Alder, Fink, Bitzer, Hosli, & Holzgreve. (2007). Depression and anxiety during pregnancy: A risk factor for obstetric, fetal and neonatal outcome. *A critical review of the literature. J Matern Fetal Neonatal Med*, 20(3), 189-209.
- Alfano, Beidel, Turner, & Lewin. (2006). Preliminary evidence for sleep complaints among children referred for anxiety. *Sleep Medicine*, 7(6), 467-473.
- Allebrandt, Teder-Laving, Akyol, Pichler, Müller-Myhsok, Pramstaller, . . . Roenneberg. (2010). Clock gene variants associate with sleep duration in two independent populations. *Biological psychiatry*, 67(11), 1040.
- Ambrosius, Lietzenmaier, Wehrle, Wichniak, Kalus, Winkelmann, . . . Friess. (2008). Heritability of sleep electroencephalogram. *Biological psychiatry*, 64(4), 344-348.
- American Psychiatric Association. (1994). *Dsm-iv: Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, D.C.
- Amin, Crawford, & Gaddum. (1954). The distribution of substance p and 5-hydroxytryptamine in the central nervous system of the dog. *The Journal of Physiology*, 126(3), 596.
- Ancoli-Israel, Cole, Alessi, Chambers, Moorcroft, & Pollak. (2003). The role of actigraphy in the study of sleep and circadian rhythms. American academy of sleep medicine review paper. *Sleep*, 26(3), 342-392.
- Anders, & Keener. (1985). Developmental course of nighttime sleep-wake patterns in full-term and premature infants during the first year of life: I. *Sleep: Journal of Sleep Research & Sleep Medicine*.
- Ando, Nonaka, Ozaki, Sato, Fujisawa, Suzuki, . . . Kato. (2006). The tokyo twin cohort project: Overview and initial findings. *Twin Research and Human Genetics*, 9(6), 817-826.
- Andretic, Franken, & Tafti. (2008). Genetics of sleep. *Annual review of genetics*, 42, 361-388.
- Araya, Hu, Heron, Enoch, Evans, Lewis, . . . Goldman. (2009). Effects of stressful life events, maternal depression and 5 htlpr genotype on emotional symptoms in pre adolescent children. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 150(5), 670-682.
- Archer, Robilliard, Skene, Smits, Williams, Arendt, & von Schantz. (2003). A length polymorphism in the circadian clock gene per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep*, 26(4), 413-415.
- Armitage. (2007). Sleep and circadian rhythms in mood disorders. *Acta Psychiatrica Scandinavica*, 115(s433), 104-115.

- Armitage, Flynn, Hoffmann, Vazquez, Lopez, & Marcus. (2009). Early developmental changes in sleep in infants: The impact of maternal depression. *Sleep*, 32(5), 693.
- Armstrong, O'Donnell, McCallum, & Dadds. (1998). Childhood sleep problems: Association with prenatal factors and maternal distress/depression. *Journal of Paediatrics and Child Health*, 34(3), 263-266.
- Astill, Van der Heijden, Van IJendoorn, & Van Someren. (2012). Sleep, cognition, and behavioral problems in school-age children: A century of research meta-analyzed.
- Austin, Hadzi-Pavlovic, Leader, Saint, & Parker. (2005). Maternal trait anxiety, depression and life event stress in pregnancy: Relationships with infant temperament. *Early Human Development*, 81(2), 183-190.
- Baird, Hill, Kendrick, & Inskip. (2009). Infant sleep disturbance is associated with preconceptional psychological distress: Findings from the southampton women's survey. *Sleep*, 32(4), 566.
- Bakermans-Kranenburg, & Van IJendoorn. (2006). Gene-environment interaction of the dopamine d4 receptor (drd4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology*, 48(5), 406-409.
- Bakermans-Kranenburg, & Van IJendoorn. (2007). Research review: Genetic vulnerability or differential susceptibility in child development: The case of attachment. *Journal of Child Psychology and Psychiatry*, 48(12), 1160-1173.
- Balsara, Faerber, Spinner, & Feudtner. (2013). Pediatric mortality in males versus females in the united states, 1999–2008. *Pediatrics*, peds. 2013-0339.
- Barbazanges, Piazza, Le Moal, & Maccari. (1996). Maternal glucocorticoid secretion mediates long-term effects of prenatal stress. *The Journal of neuroscience*, 16(12), 3943-3949.
- Barclay, Eley, Mill, Wong, Zavos, Archer, & Gregory. (2011). Sleep quality and diurnal preference in a sample of young adults: Associations with 5httlpr, per3, and clock 3111. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*.
- Barker. (2001). Fetal and infant origins of adult disease. *Monatsschrift Kinderheilkunde*, 149(13), 2-6.
- Barker, & Osmond. (1986). Infant mortality, childhood nutrition, and ischaemic heart disease in england and wales. *The Lancet*, 327(8489), 1077-1081.
- Barnett, Xu, Heron, Goldman, & Jones. (2010). Cognitive effects of genetic variation in monoamine neurotransmitter systems: A population based study of comt, maoa, and 5httlpr. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*.
- Barr, Bookstein, O'Malley, Connor, Huggins, & Streissguth. (2006). Binge drinking during pregnancy as a predictor of psychiatric disorders on the structured clinical interview for dsm-iv in young adult offspring. *American Journal of Psychiatry*, 163(6), 1061-1065.
- Bartels, de Geus, Kirschbaum, Sluyter, & Boomsma. (2003). Heritability of daytime cortisol levels in children. *Behavior genetics*, 33(4), 421-433.
- Batenburg-Eddes, Brion, Henrichs, Jaddoe, Hofman, Verhulst, . . . Tiemeier. (2012). Parental depressive and anxiety symptoms during pregnancy and attention problems in children: A cross-cohort consistency study. *Journal of Child Psychology and Psychiatry*.

- Bates, Freeland, & Lounsbury. (1979). Measurement of infant difficultness. *Child Development*, 50(3), 794-803.
- Beddoe, Paul Yang, Kennedy, Weiss, & Lee. (2009). The effects of mindfulness-based yoga during pregnancy on maternal psychological and physical distress. *Journal of Obstetric, Gynecologic, & Neonatal Nursing*, 38(3), 310-319.
- Beebe, & Lee. (2007). Sleep disturbance in late pregnancy and early labor. *The Journal of Perinatal & Neonatal Nursing*, 21(2), 103-108.
- Belsky. (1997a). Theory testing, effect-size evaluation, and differential susceptibility to rearing influence: The case of mothering and attachment. *Child Development*, 68(4), 598-600.
- Belsky. (1997b). Variation in susceptibility to environmental influence: An evolutionary argument. *Psychological Inquiry*, 8(3), 182-186.
- Belsky. (2005). Differential susceptibility to rearing influence. *Origins of the social mind: Evolutionary psychology and child development*, 139-163.
- Belsky, Bakermans-Kranenburg, & Van IJzendoorn. (2007). For better and for worse. *Current Directions in Psychological Science*, 16(6), 300.
- Belsky, Jonassaint, Pluess, Stanton, Brummett, & Williams. (2009). Vulnerability genes or plasticity genes? *Molecular psychiatry*, 14(8), 746-754.
- Belsky, & Pluess. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological bulletin*, 135(6), 885-908.
- Benedetti, Dallaspezia, Fulgosi, Lorenzi, Serretti, Barbini, . . . Smeraldi. (2007). Actimetric evidence that clock 3111 t/c snp influences sleep and activity patterns in patients affected by bipolar depression. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 144(5), 631-635.
- Benedetti, Serretti, Colombo, Campori, Barbini, di Bella, & Smeraldi. (1999). Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. *American Journal of Psychiatry*, 156(9), 1450-1452.
- Bennett, Einarson, Taddio, Koren, & Einarson. (2004). Prevalence of depression during pregnancy: Systematic review. *Obstetrics & Gynecology*, 103(4), 698.
- Berger, Gray, & Roth. (2009). The expanded biology of serotonin. *Annual review of medicine*, 60, 355-366.
- Bergman, Sarkar, O'Connor, Modi, & Glover. (2007). Maternal stress during pregnancy predicts cognitive ability and fearfulness in infancy. *J Am Acad Child Adolesc Psychiatry*, Nov;46(11), 1454-1463.
- Bernier, Beauchamp, Bouvette-Turcot, Carlson, & Carrier. (2013). Sleep and cognition in preschool years: Specific links to executive functioning. *Child development*.
- Bernier, Bélanger, Bordeleau, & Carrier. (2012). Mothers, fathers, and toddlers: Parental psychosocial functioning as a context for young children's sleep.
- Bernier, Carlson, Bordeleau, & Carrier. (2010). Relations between physiological and cognitive regulatory systems: Infant sleep regulation and subsequent executive functioning. *Child development*, 81(6), 1739-1752.
- Bolten, Wurmser, Buske-Kirschbaum, Papoušek, Pirke, & Hellhammer. (2011). Cortisol levels in pregnancy as a psychobiological predictor for birth weight. *Archives of women's mental health*, 14(1), 33-41.
- Bonzini, Palmer, Coggon, Carugno, Cromi, & Ferrario. (2011). Shift work and pregnancy outcomes: A systematic review with meta-analysis of currently available epidemiological studies. *BJOG: An International Journal of Obstetrics & Gynaecology*, 118(12), 1429-1437.

- Boyce, & Ellis. (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and psychopathology*, 17(2), 271-301.
- Boyce, Stubbs, & Todd. (1993). The edinburgh postnatal depression scale: Validation for an australian sample. *Australian and New Zealand Journal of Psychiatry*, 27(3), 472 - 476.
- Boyd, Golding, Macleod, Lawlor, Fraser, Henderson, . . . Smith. (2012). Cohort profile: The 'children of the 90s'—the index offspring of the avon longitudinal study of parents and children. *International Journal of Epidemiology*.
- Bradley, & Corwyn. (2008). Infant temperament, parenting, and externalizing behavior in first grade: A test of the differential susceptibility hypothesis. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 49, 124-131.
- Braithwaite, Ramchandani, O'Connor, van IJzendoorn, Bakermans-Kranenburg, Glover, . . . Murphy. (2013). No moderating effect of 5-HTTLPR on associations between antenatal anxiety and infant behavior. *Journal of the American Academy of Child & Adolescent Psychiatry*.
- Brescianini, Volzone, Fagnani, Patriarca, Grimaldi, Lanni, . . . Stazi. (2011). Genetic and environmental factors shape infant sleep patterns: A study of 18-month-old twins. *Pediatrics*, 127(5), e1296-e1302.
- Brugha. (2010). Pregnancy and wellbeing study (paws) Retrieved 5 November 2012, from www.controlled-trials.com
- Brummett, Krystal, Ashley-Koch, Kuhn, Züchner, Siegler, . . . Williams. (2007). Sleep quality varies as a function of 5-HTTLPR genotype and stress. *Psychosomatic Medicine*, 69(7), 621-624.
- Brzustowicz, & Freedman. (2011). Digging more deeply for genetic effects in psychiatric illness. *American Journal of Psychiatry*, 168(10), 1017-1020.
- Bub, Buckhalt, & El-Sheikh. (2011). Children's sleep and cognitive performance: A cross-domain analysis of change over time. *Developmental psychology*, 47(6), 1504.
- Burke, Davis, Otte, & Mohr. (2005). Depression and cortisol responses to psychological stress: A meta-analysis. *Psychoneuroendocrinology*, 30(9), 846-856.
- Burns, Baxter, Bennert, Wiles, Ramchandani, Turner, . . . Evans. (2013). A pilot randomised controlled trial of cognitive behavioural therapy for antenatal depression. *BMC Psychiatry*, 13(1), 33.
- Buysse, & Reynolds. (1989). The pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry research*, 28(2), 193-213.
- Carey. (1974). Night waking and temperament in infancy. *The Journal of pediatrics*, 84(5), 756-758.
- Carey, & McDevitt. (1978). Revision of the infant temperament questionnaire. *Pediatrics*, 61(5), 735-739.
- Carpen, Von Schantz, Smits, Skene, & Archer. (2006). A silent polymorphism in the PER1 gene associates with extreme diurnal preference in humans. *Journal of human genetics*, 51(12), 1122-1125.
- Carroll, Denenberg, & Thoman. (1999). A comparative study of quiet sleep, active sleep, and waking on the first 2 days of life. *Developmental Psychobiology*, 35(1), 43-48.
- Caspi, Sugden, Moffitt, Taylor, Craig, Harrington, . . . Braithwaite. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, 301(5631), 386.

- Celedonia. (2009). *Mindfulness-based interventions for antenatal depression or anxiety: Perspectives of midwives*. University of Pittsburgh.
- Chang, Chen, & Huang. (2008). Effects of music therapy on psychological health of women during pregnancy. *Journal of clinical nursing*, 17(19), 2580-2587.
- Chang, Pien, Duntley, & Macones. (2010). Sleep deprivation during pregnancy and maternal and fetal outcomes: Is there a relationship? *Sleep medicine reviews*, 14(2), 107-114.
- Chapillon, Patin, Roy, Vincent, & Caston. (2002). Effects of pre-and postnatal stimulation on developmental, emotional, and cognitive aspects in rodents: A review. *Developmental psychobiology*, 41(4), 373-387.
- Chipman, Jorm, Prior, Sanson, Smart, Tan, & Easteal. (2007). No interaction between the serotonin transporter polymorphism (5-HTTLPR) and childhood adversity or recent stressful life events on symptoms of depression: Results from two community surveys. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 144(4), 561-565.
- Copeland, Adair, Smetanin, Stiff, Briante, Colman, . . . Angold. (2013). Diagnostic transitions from childhood to adolescence to early adulthood. *Journal of Child Psychology and Psychiatry*.
- Cox, Chapman, Murray, & Jones. (1995). Validation of the Edinburgh postnatal depression scale (EPDS) in non-postnatal women. *Journal of Affective Disorders*, 39, 185-189.
- Cox, Chapman, Murray, & Jones. (1996). Validation of the Edinburgh postnatal depression scale (EPDS) in non-postnatal women. *Journal of affective disorders*, 39(3), 185-189.
- Cox, Holden, & Sagovsky. (1987). Detection of postnatal depression: Development of the 10 item Edinburgh postnatal depression scale. *British Journal of Psychiatry*, 150, 782-786.
- Crosby, LeBourgeois, & Harsh. (2005). Racial differences in reported napping and nocturnal sleep in 2-to 8-year-old children. *Pediatrics*, 115(Supplement 1), 225-232.
- Dahl. (1996). The regulation of sleep and arousal: Development and psychopathology. *Development and Psychopathology*, 8, 3-28.
- Dahl, & Harvey. (2007). Sleep in children and adolescents with behavioral and emotional disorders. *Sleep Medicine Clinics*, 2(3), 501-511.
- Dahl, Pelham, & Wiersma. (1991). The role of sleep disturbances in attention deficit disorder symptoms: A case study. *Journal of Pediatric Psychology*, 16(2), 229-239.
- Damon (Ed.). (1998). *Handbook of child psychology* (5th edition ed.). New York: John Wiley & Sons.
- Davis, Glynn, Dunkel Schetter, Hobel, Chicz-Demet, & Sandman. (2005). Corticotropin-releasing hormone during pregnancy is associated with infant temperament. *Developmental neuroscience*, 27(5), 299-305.
- Davis, Glynn, Schetter, Hobel, Chicz-Demet, & Sandman. (2007a). Prenatal exposure to maternal depression and cortisol influences infant temperament. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46(6), 737-746.
- Davis, Glynn, Schetter, Hobel, Chicz-Demet, & Sandman. (2007b). Prenatal exposure to maternal depression and cortisol influences infant temperament. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46(6), 737-746.

- Davis, Snidman, Wadhwa, Glynn, Schetter, & Sandman. (2004). Prenatal maternal anxiety and depression predict negative behavioral reactivity in infancy. *Infancy*, 6(3), 319-331.
- Dawes, Fox, Leduc, Liggins, & Richards. (1972). Respiratory movements and rapid eye movement sleep in the foetal lamb. *The Journal of Physiology*, 220(1), 119.
- De Beurs. (2004). *Brief symptom inventory, handleiding (manual)*. Leiden, The Netherlands: Pits Publishers.
- de Bruijn, van Bakel, Wijnen, Pop, & van Baar. (2009). Prenatal maternal emotional complaints are associated with cortisol responses in toddler and preschool aged girls. *Developmental psychobiology*, 51(7), 553-563.
- De Gennaro, Marzano, Fratello, Moroni, Pellicciari, Ferlazzo, . . . Sforza. (2008). The electroencephalographic fingerprint of sleep is genetically determined: A twin study. *Annals of neurology*, 64(4), 455-460.
- de Weerd, & van den Bossche. (2003). The development of sleep during the first months of life. *Sleep medicine reviews*, 7(2), 179-191.
- de Weerth, van Hees, & Buitelaar. (2003). Prenatal maternal cortisol levels and infant behavior during the first 5 months. *Early human development*, 74(2), 139-151.
- Dearing, McCartney, Marshall, & Warner. (2001). Parental reports of children's sleep and wakefulness: Longitudinal associations with cognitive and language outcomes. *Infant Behavior and Development*, 24(2), 151-170.
- Deave, Heron, Evans, & Emond. (2008). The impact of maternal depression in pregnancy on early child development. *BJOG, Jul;115(8)*(1043-51).
- Dennis, & Allen. (2008). Interventions (other than pharmacological, psychosocial or psychological) for treating antenatal depression. *Cochrane Database Syst Rev*, 4.
- Dennis, & Ross. (2005). Relationships among infant sleep patterns, maternal fatigue, and development of depressive symptomatology. *Birth*, 32(3), 187-193.
- Dennis, Ross, & Grigoriadis. (2007). Psychosocial and psychological interventions for treating antenatal depression. *Cochrane Database Syst Rev*, 3.
- Derogatis, & Melisaratos. (1983). The brief symptom inventory: An introductory report. *Psychological Medicine*, 13(03), 595-605.
- Deuschle, Schredl, Schilling, Wüst, Frank, Witt, . . . Schulze. (2010). Association between a serotonin transporter length polymorphism and primary insomnia. *Sleep*, 33(3), 343.
- Dewald, Meijer, Oort, Kerkhof, & Bögels. (2010). The influence of sleep quality, sleep duration and sleepiness on school performance in children and adolescents: A meta-analytic review. *Sleep medicine reviews*, 14(3), 179-189.
- Di Renzo, Rosati, Sarti, Cruciani, & Cutuli. (2007). Does fetal sex affect pregnancy outcome? *Gender medicine*, 4(1), 19-30.
- Diego, Field, & Hernandez-Reif. (2005). Prepartum, postpartum and chronic depression effects on neonatal behavior. *Infant Behavior and Development*, 28(2), 155-164.
- Dieter, Field, Hernandez-Reif, Jones, Lecanuet, Salman, & Redzepi. (2001). Maternal depression and increased fetal activity. *Journal of Obstetrics and Gynaecology*, 21(5), 468 - 473.
- Dionne, Touchette, Forget-Dubois, Petit, Tremblay, Montplaisir, & Boivin. (2011). Associations between sleep-wake consolidation and language development in early childhood: A longitudinal twin study. *Sleep*, 34(8), 987.
- DiPietro, Ghera, & Costigan. (2008). Prenatal origins of temperamental reactivity in early infancy. *Early human development*, 84(9), 569-575.

- Doornbos, van Goor, Dijck-Brouwer, Schaafsma, Korf, & Muskiet. (2009). Supplementation of a low dose of dha or dha+ aa does not prevent peripartum depressive symptoms in a small population based sample. *Progress in neuro-psychopharmacology & biological psychiatry*, 33(1), 49.
- Dørheim, Bondevik, Eberhard-Gran, & Bjorvatn. (2009). Sleep and depression in postpartum women: A population-based study. *Sleep*, 32(7), 847.
- Dougherty, Smith, Olino, Dyson, Bufferd, Rose, & Klein. (2013). Maternal psychopathology and early child temperament predict young children's salivary cortisol 3 years later. *Journal of abnormal child psychology*, 1-12.
- Dugovic, Maccari, Weibel, & Turek. (1999). High corticosterone levels in prenatally stressed rats predict persistent paradoxical sleep alterations. *Journal of Neuroscience*, 19(19), 8656.
- Duncan. (2013). Paying attention to all results, positive and negative. *Journal of the American Academy of Child and Adolescent Psychiatry*, 52(5), 462-465.
- Duncan, & Keller. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *The American journal of psychiatry*, 168(10), 1041.
- Dunn, Hanieh, Roberts, & Powrie. (2012). Mindful pregnancy and childbirth: Effects of a mindfulness-based intervention on women's psychological distress and well-being in the perinatal period. *Archives of women's mental health*, 15(2), 139-143.
- Dunn, Uddin, Subramanian, Smoller, Galea, & Koenen. (2011). Research review: Gene-environment interaction research in youth depression—a systematic review with recommendations for future research. *Journal of Child Psychology and Psychiatry*.
- Ebisawa, Uchiyama, Kajimura, Mishima, Kamei, Katoh, . . . Kim. (2001). Association of structural polymorphisms in the human period3 gene with delayed sleep phase syndrome. *EMBO reports*, 2(4), 342-346.
- Edmondson, Psychogiou, Vlachos, Netsi, & Ramchandani. (2010). Depression in fathers in the postnatal period: Assessment of the edinburgh postnatal depression scale as a screening measure. *Journal of Affective Disorders*, 125(1-3), 365-368. doi: DOI: 10.1016/j.jad.2010.01.069
- Ednick, Cohen, McPhail, Beebe, Simakajornboon, & Amin. (2009). A review of the effects of sleep during the first year of life on cognitive, psychomotor, and temperament development. *Sleep*, 32(11), 1449.
- El-Sheikh, Harger, & Whitson. (2001). Exposure to interparental conflict and children's adjustment and physical health: The moderating role of vagal tone. *Child development*, 72(6), 1617-1636.
- El Marroun, Jaddoe, Hudziak, Roza, Steegers, Hofman, . . . Tiemeier. (2012). Maternal use of selective serotonin reuptake inhibitors, fetal growth, and risk of adverse birth outcomes. *Archives of general psychiatry*, archgenpsychiatry. 2011.2333 v2011.
- Ellis, & Boyce. (2008). Biological sensitivity to context. *Current Directions in Psychological Science*, 17(3), 183-187.
- Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn. (2011). Differential susceptibility to the environment: An evolutionary--neurodevelopmental theory. *Development and psychopathology*, 23(1), 7-28.
- Ellis, Essex, & Boyce. (2005). Biological sensitivity to context: Ii. Empirical explorations of an evolutionary--developmental theory. *Development and psychopathology*, 17(02), 303-328.

- Emory, & Dieter. (2006). Maternal depression and psychotropic medication effects on the human fetus. *Annals of the New York Academy of Sciences*, 1094(1), 287-291.
- Epperson, Terman, Terman, Hanusa, Oren, Peindl, & Wisner. (2004). Randomized clinical trial of bright light therapy for antepartum depression: Preliminary findings. *Journal of Clinical Psychiatry*, 65(3), 421-425.
- Epstein, Chillag, & Lavie. (1998). Starting times of school: Effects on daytime functioning of fifth grade children in israel. *Sleep*, 21(3), 250-257.
- Evans, Heron J., Francomb H., Oke S., & Golding J. (2001). Cohort study of depressed mood during pregnancy and after childbirth. *BMJ*, Aug 4;323(7307), 257-260.
- Fallone, Acebo, Arnedt, Seifer, & Carskadon. (2001). Effects of acute sleep restriction on behavior, sustained attention, and response inhibition in children. *Perceptual and motor skills*, 93(1), 213-229.
- Fallone, Acebo, Seifer, & Carskadon. (2005). Experimental restriction of sleep opportunity in children: Effects on teacher ratings. *Sleep*, 28(12), 1561.
- Fenger-Grøn, Thomsen, Andersen, & Nielsen. (2011). Paediatric outcomes following intrauterine exposure to serotonin reuptake inhibitors: A systematic review. *Danish Medical Bulletin (Online)*, 58(9).
- Fergusson, Horwood, Miller, & Kennedy. (2011). Life stress, 5-httlpr and mental disorder: Findings from a 30-year longitudinal study. *The British Journal of Psychiatry*, 198(2), 129-135.
- Field. (2006). Prenatal depression effects on the fetus and newborn: A review. *Infant Behavior & Development*, 29(3), 445.
- Field. (2011). Prenatal depression effects on early development: A review. *Infant behavior and development*, 34(1), 1-14.
- Field, Deeds, Diego, Hernandez-Reif, Gauler, Sullivan, . . . Nearing. (2009). Benefits of combining massage therapy with group interpersonal psychotherapy in prenatally depressed women. *Journal of bodywork and movement therapies*, 13(4), 297-303.
- Field, & Diego. (2008). Cortisol: The culprit prenatal stress variable. *International Journal of Neuroscience*, 118(8), 1181-1205.
- Field, Diego, Dieter, Hernandez-Reif, Schanberg, Kuhn, . . . Bendell. (2004). Prenatal depression effects on the fetus and the newborn. *Infant Behavior and Development*, 27(2), 216-229.
- Field, Diego, & Hernandez-Reif. (2006). Prenatal depression effects on the fetus and newborn: A review. *Infant Behavior and Development*, 29(3), 445-455.
- Field, Diego, Hernandez-Reif, Figueiredo, Schanberg, & Kuhn. (2007). Sleep disturbances in depressed pregnant women and their newborns. *Infant Behavior and Development*, 30(1), 127-133.
- Field, Diego, Hernandez-Reif, Medina, Delgado, & Hernandez. (2011). Yoga and massage therapy reduce prenatal depression and prematurity. *Journal of Bodywork and Movement Therapies*.
- Field, Diego, Hernandez-Reif, Schanberg, & Kuhn. (2004). Massage therapy effects on depressed pregnant women. *Journal of Psychosomatic Obstetrics & Gynecology*, 25(2), 115-122.
- Field, Figueiredo, Hernandez-Reif, Diego, Deeds, & Ascencio. (2008). Massage therapy reduces pain in pregnant women, alleviates prenatal depression in both parents and improves their relationships. *Journal of Bodywork and Movement Therapies*, 12(2), 146-150.

- First, Spitzer, Gibbon, & Williams. (2002). *Structured clinical interview for dsm-iv-tr axis i disorders, research version, patient edition. (scid-i/p)* New York: Biometrics Research, New York State Psychiatric Institute.
- Fisher, van Jaarsveld, Llewellyn, & Wardle. (2012). Genetic and environmental influences on infant sleep. *Pediatrics*, 129(6), 1091-1096.
- Flynn, Blow, & Marcus. (2006). Rates and predictors of depression treatment among pregnant women in hospital-affiliated obstetrics practices. *General hospital psychiatry*, 28(4), 289-295.
- Foley, Eaves, Wormley, Silberg, Maes, Kuhn, & Riley. (2004). Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. *Archives of General Psychiatry*, 61(7), 738.
- Frank, & Benington. (2006). The role of sleep in memory consolidation and brain plasticity: Dream or reality? *The Neuroscientist*, 12(6), 477-488.
- Fredriksen, Rhodes, Reddy, & Way. (2004). Sleepless in chicago: Tracking the effects of adolescent sleep loss during the middle school years. *Child development*, 75(1), 84-95.
- Freeman. (2007). Antenatal depression: Navigating the treatment dilemmas. *American Journal of Psychiatry*, 164(8), 1162-1165.
- Freeman, & Davis. (2010). Supportive psychotherapy for perinatal depression: Preliminary data for adherence and response. *Depression and anxiety*, 27(1), 39-45.
- Freeman, Davis, Sinha, Wisner, Hibbeln, & Gelenberg. (2008). Omega-3 fatty acids and supportive psychotherapy for perinatal depression: A randomized placebo-controlled study. *Journal of affective disorders*, 110(1), 142-148.
- Frodl, Meisenzahl, Zill, Baghai, Rujescu, Leinsinger, . . . Engel. (2004). Reduced hippocampal volumes associated with the long variant of the serotonin transporter polymorphism in major depression. *Archives of general psychiatry*, 61(2), 177.
- Galland, Taylor, Elder, & Herbison. (2012). Normal sleep patterns in infants and children: A systematic review of observational studies. *Sleep Medicine Reviews*, 16(3), 213-222.
- Gartstein, & Rothbart. (2003). Studying infant temperament via the revised infant behavior questionnaire. *Infant Behavior and Development*, 26(1), 64-86.
- Gaynes, Gavin, Meltzer-Brody, Lohr, Swinson, Gartlehner, . . . Miller. (2005). Perinatal depression: Prevalence, screening accuracy, and screening outcomes: Summary.
- Gerardin, Wendland, Bodeau, Galin, Bialobos, Tordjman, . . . Dommergues. (2011). Depression during pregnancy: Is the developmental impact earlier in boys? A prospective case-control study. *Journal of Clinical Psychiatry*, 72(3), 378.
- Gilissen, Bakermans-Kranenburg, Van IJzendoorn, & Van Der Veer. (2008). Parent-child relationship, temperament, and physiological reactions to fear-inducing film clips: Further evidence for differential susceptibility. *Journal of Experimental Child Psychology*, 99(3), 182-195.
- Gitau, Fisk, & Glover. (2001). Maternal stress in pregnancy and its effect on the human foetus: An overview of research findings. *Stress: The International Journal on the Biology of Stress*, 4(3), 195-203.
- Gitau, Fisk, Teixeira, Cameron, & Glover. (2001). Fetal hypothalamic-pituitary-adrenal stress responses to invasive procedures are independent of maternal responses. *Journal of Clinical Endocrinology & Metabolism*, 86(1), 104-109.

- Glover. (2011). Annual research review: Prenatal stress and the origins of psychopathology: An evolutionary perspective. *Journal of Child Psychology and Psychiatry*, 52(4), 356-367.
- Glover, Bergman, Sarkar, & O'Connor. (2009). Association between maternal and amniotic fluid cortisol is moderated by maternal anxiety. *Psychoneuroendocrinology*, 34(3), 430-435.
- Glover, & Hill. (2012). Sex differences in the programming effects of prenatal stress on psychopathology and stress responses: An evolutionary perspective. *Physiology & behavior*, 106(5), 736-740.
- Glover, O'Connor, & O'Donnell. (2010). Prenatal stress and the programming of the hpa axis. *Neuroscience & Biobehavioral Reviews*, 35(1), 17-22.
- Gluckman, & Hanson. (2005). *The fetal matrix: Evolution, development and disease*: Cambridge University Press.
- Gluckman, & Hanson. (2006). *Mismatch: Why our world no longer fits our bodies: Why our world no longer fits our bodies*: Oxford University Press.
- Gluckman, Hanson, Cooper, & Thornburg. (2008). Effect of in utero and early-life conditions on adult health and disease. *New England Journal of Medicine*, 359(1), 61-73.
- Gluckman, Hanson, Spencer, & Bateson. (2005). Environmental influences during development and their later consequences for health and disease: Implications for the interpretation of empirical studies. *Proc Biol Sci, Apr 7*; (272(1564)), 671-677.
- Goedhart, Vrijkotte, Roseboom, van der Wal, Cuijpers, & Bonsel. (2010). Maternal cortisol and offspring birthweight: Results from a large prospective cohort study. *Psychoneuroendocrinology*, 35(5), 644-652.
- Gomez, Newman-Smith, Breslin, & Bootzin. (2011). Learning, memory and sleep in children. *Sleep Med Clin*, 6(1), 45-57.
- Goodman, Corcoran, Turner, Yuan, & Green. (1998). Assessing traumatic event exposure: General issues and preliminary findings for the stressful life events screening questionnaire. *Journal of Traumatic Stress*, 11(3), 521-542.
- Gottesman, & Shields. (1967). A polygenic theory of schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, 58(1), 199.
- Gould. (1999). Serotonin and hippocampal neurogenesis. *Neuropsychopharmacology*, 21(2), 46S-51S.
- Gregory, Caspi, Eley, Moffitt, O'Connor, & Poulton. (2005). Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. *Journal of Abnormal Child Psychology*, 33(2), 157-163.
- Gregory, Eley, O'Connor, & Plomin. (2004). Etiologies of associations between childhood sleep and behavioral problems in a large twin sample. *Journal of the American Academy of Child & Adolescent Psychiatry*, 43(6), 744-751.
- Gregory, & Franken. (2009). Genetic approaches to the problem of sleep.
- Gregory, Rijdsdijk, & Eley. (2006). A twin-study of sleep difficulties in school-aged children. *Child Development*, 77(6), 1668-1679. doi: 10.1111/j.1467-8624.2006.00966.x
- Gregory, & Sadeh. (2012). Sleep, emotional and behavioral difficulties in children and adolescents. *Sleep Medicine Reviews*, 16(2), 129-136.
- Grote. (2010). Momcare: Culturally relevant treatment services for perinatal depression Retrieved 5 November 2012, from www.controlled-trials.com

- Grote, Bridge, Gavin, Melville, Iyengar, & Katon. (2010). A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Archives of general psychiatry*, 67(10), 1012.
- Grote, Swartz, Geibel, Zuckoff, Houck, & Frank. (2009). A randomized controlled trial of culturally relevant, brief interpersonal psychotherapy for perinatal depression. *Psychiatric services (Washington, DC)*, 60(3), 313.
- Guerin, & Gottfried. (1994). Temperamental consequences of infant difficultness. *Infant Behavior and Development*, 17(4), 413-421.
- Gutteling, Weerth, & Buitelaar. (2005). Prenatal stress and children's cortisol reaction to the first day of school. *Psychoneuroendocrinology*, 30(6), 541-549.
- Halpern, Anders, Garcia Coll, & Hua. (1994). Infant temperament: Is there a relation to sleep-wake states and maternal nighttime behavior? *Infant Behavior and Development*, 17(3), 255-263.
- Harris, Huckle, Thomas, & Johns. (1989). The use of rating scales to identify post-natal depression. *British Journal of Psychiatry*, 154, 813-817.
- Harrison, & Horne. (2000). The impact of sleep deprivation on decision making: A review. *Journal of Experimental Psychology: Applied*, 6(3), 236.
- Hay, Pawlby, Waters, Perra, & Sharp. (2010). Mothers' antenatal depression and their children's antisocial outcomes. *Child Development*, 81(1), 149-165.
- Hayes, McCoy, Fukumizu, Wellman, & DiPietro. (2011). Temperament and sleep-wake behaviour from infancy to toddlerhood. *Infant and child development*, 20(5), 495-508.
- Hayes, Muller, & Bradley. (2001). Perinatal depression: A randomized controlled trial of an antenatal education intervention for primiparas. *Birth*, 28(1), 28-35.
- Health. (2007). *Antenatal and postnatal mental health: The nice guideline on clinical management and service guidance* (Vol. 45). Leicester (UK).
- Heath, Eaves, Kirk, & Martin. (1998). Effects of lifestyle, personality, symptoms of anxiety and depression, and genetic predisposition on subjective sleep disturbance and sleep pattern. *Twin Research*, 1(4), 176-188.
- Heikkinen, Ekblad, & Laine. (2002). Transplacental transfer of citalopram, fluoxetine and their primary demethylated metabolites in isolated perfused human placenta. *BJOG: An International Journal of Obstetrics & Gynaecology*, 109(9), 1003-1008.
- Heinz, Jones, Mazzanti, Goldman, Ragan, Hommer, . . . Weinberger. (2000). A relationship between serotonin transporter genotype and in vivo protein expression and alcohol neurotoxicity. *Biological psychiatry*, 47(7), 643-649.
- Hemmi, Wolke, & Schneider. (2011). Associations between problems with crying, sleeping and/or feeding in infancy and long-term behavioural outcomes in childhood: A meta-analysis. *Archives of disease in childhood*, 96(7), 622-629.
- Hendrick, Stowe, Altshuler, Hwang, Lee, & Haynes. (2003). Placental passage of antidepressant medications. *American Journal of Psychiatry*, 160(5), 993-996.
- Henrichs, Schenk, Roza, Van den Berg, Schmidt, Steegers, . . . Tiemeier. (2010). Maternal psychological distress and fetal growth trajectories: The generation r study. *Psychol Med*, 40(4), 633-643.
- Heraghty, Hilliard, Henderson, & Fleming. (2008). The physiology of sleep in infants. *Archives of disease in childhood*, 93(11), 982-985.
- Higgins, Green, & Collaboration. (2008). *Cochrane handbook for systematic reviews of interventions* (Vol. 5): Wiley Online Library.
- Hill. (1965). The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine*, 58(5), 295.

- Hiscock, Canterford, Ukoumunne, & Wake. (2007). Adverse associations of sleep problems in australian preschoolers: National population study. *Pediatrics*, 119(1), 86-93.
- Homberg, & Lesch. (2010). Looking on the bright side of serotonin transporter gene variation. *Biological psychiatry*.
- Hoppenbrouwers, Ugartechea, & Combs. (1978). Studies of maternal-fetal interaction during the last trimester of pregnancy: Ontogenesis of the basic rest-activity cycle. *Experimental Neurology*, 61(1), 136-153.
- Hu, Lipsky, Zhu, Akhtar, Taubman, Greenberg, . . . Kennedy. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *The American Journal of Human Genetics*, 78(5), 815-826.
- Hu, Oroszi, Chun, Smith, Goldman, & Schuckit. (2005). An expanded evaluation of the relationship of four alleles to the level of response to alcohol and the alcoholism risk. *Alcoholism: Clinical and Experimental Research*, 29(1), 8-16.
- Hublin, Kaprio, Partinen, & Koskenvuo. (2001). Parasomnias: Co-occurrence and genetics. *Psychiatric genetics*, 11(2), 65-70.
- Hudson, Gradisar, Gamble, Schniering, & Rebelo. (2009). The sleep patterns and problems of clinically anxious children. *Behaviour research and therapy*, 47(4), 339-344.
- Huizink, Robles de Medina, Mulder, Visser, & Buitelaar. (2002). Psychological measures of prenatal stress as predictors of infant temperament. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41(9), 1078-1085.
- IBM. (2011). Ibm spss statistics for windows (Version 20.0). NY: IBM Corp.
- Ingemarsson. (2003). Gender aspects of preterm birth. *BJOG: An International Journal of Obstetrics & Gynaecology*, 110(s20), 34-38.
- Jaddoe, van Duijn, van der Heijden, Mackenbach, Moll, Steegers, . . . Hofman. (2008). The generation r study: Design and cohort update until the age of 4 years. *European journal of epidemiology*, 23(12), 801-811.
- Jansen, Saridjan, Hofman, Jaddoe, Verhulst, & Tiemeier. (2011). Does disturbed sleeping precede symptoms of anxiety or depression in toddlers? The generation r study. *Psychosomatic Medicine*, 73(3), 242-249.
- Jimmerson. (1991). Maternal, environmental, and temperamental characteristics of toddlers with and toddlers without sleep problems. *Journal of Pediatric Health Care*, 5(2), 71-77.
- Johanson, Chapman, Murray, Johnson, & Cox. (2000). The north staffordshire maternity hospital prospective study of pregnancy-associated depression. *Journal of Psychosomatic Obstetrics & Gynecology*, 21(2), 93-97.
- Johnson, Roth, & Breslau. (2006). The association of insomnia with anxiety disorders and depression: Exploration of the direction of risk. *Journal of Psychiatric Research; Journal of Psychiatric Research*.
- Jomeen, & Martin. (2007). Assessment and relationship of sleep quality to depression in early pregnancy. *Journal of Reproductive and Infant Psychology*, 25(1), 87-99.
- Jones, Field, Fox, Lundy, & Davalos. (1997). Eeg activation in 1-month-old infants of depressed mothers. *Development and Psychopathology*, 9(03), 491-505.
- Jones, Ring, Tyfield, Hamvas, Simmons, Pembrey, & Golding. (2000). A new human genetic resource: A DNA bank established as part of the avon longitudinal study of pregnancy and childhood (alspac). *European journal of human genetics: EJHG*, 8(9), 653.

- Josefsson, Berg, Nordin, & Sydsjö. (2001). Prevalence of depressive symptoms in late pregnancy and postpartum. *Acta obstetrica et gynecologica Scandinavica*, 80(3), 251-255.
- Jouvet. (1999). Sleep and serotonin:: An unfinished story. *Neuropsychopharmacology*, 21(2), 24S-27S.
- Kamysheva, Skouteris, Wertheim, Paxton, & Milgrom. (2008). Examination of a multi-factorial model of body-related experiences during pregnancy: The relationships among physical symptoms, sleep quality, depression, self-esteem, and negative body attitudes. *Body Image*, 5(2), 152-163.
- Karg, Burmeister, Shedden, & Sen. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. *Archives of general psychiatry*, 68(5), 444.
- Karraker, & Young. (2007). Night waking in 6-month-old infants and maternal depressive symptoms. *Journal of applied developmental psychology*, 28(5), 493-498.
- Katzenberg, Young, Finn, Lin, King, Takahashi, & Mignot. (1998). A clock polymorphism associated with human diurnal preference. *Sleep: Journal of Sleep Research & Sleep Medicine*.
- Keener, Zeanah, & Anders. (1988). Infant temperament, sleep organization, and nighttime parental interventions. *Pediatrics*, 81(6), 762-771.
- Kelmanson. (2000). Snoring, noisy breathing in sleep and daytime behaviour in 2–4-month-old infants. *European journal of pediatrics*, 159(10), 734-739.
- Kessler. (2003). Epidemiology of women and depression. *Journal of affective disorders*, 74(1), 5-13.
- Kessler, Berglund, Demler, Jin, Koretz, Merikangas, . . . Wang. (2003). The epidemiology of major depressive disorder. *JAMA: the journal of the American Medical Association*, 289(23), 3095-3105.
- Kim-Cohen, Caspi, Taylor, Williams, Newcombe, Craig, & Moffitt. (2006). Maltreatment, and gene–environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molecular psychiatry*, 11(10), 903-913.
- Kimura, & Winkelmann. (2007). Genetics of sleep and sleep disorders. *Cellular and molecular life sciences*, 64(10), 1216-1226.
- Kinney, Belliveau, Trachtenberg, Rava, & Paterson. (2007). The development of the medullary serotonergic system in early human life. *Autonomic Neuroscience*, 132(1), 81-102.
- Kinney, Miller, Crowley, Huang, & Gerber. (2008). Autism prevalence following prenatal exposure to hurricanes and tropical storms in Louisiana. *Journal of autism and developmental disorders*, 38(3), 481-488.
- Kiryanova, Smith, Dyck, & Antle. (2012). The effects of perinatal fluoxetine treatment on the circadian system of the adult mouse. *Psychopharmacology*, 1-9.
- Klebanoff, Shiono, & Rhoads. (1990). Outcomes of pregnancy in a national sample of resident physicians. *New England Journal of Medicine*, 323(15), 1040-1045.
- Kochanska. (1993). Toward a synthesis of parental socialization and child temperament in early development of conscience. *Child Development*, 64(2), 325-347.
- Kochanska, Aksan, & Joy. (2007). Children's fearfulness as a moderator of parenting in early socialization: Two longitudinal studies. *Developmental Psychology*, 43(1), 222.

- Kunugi, Hattori, Kato, Tatsumi, Sakai, Sasaki, . . . Nanko. (1996). Serotonin transporter gene polymorphisms: Ethnic difference and possible association with bipolar affective disorder. *Molecular psychiatry*, 2(6), 457-462.
- Lam, Hiscock, & Wake. (2003). Outcomes of infant sleep problems: A longitudinal study of sleep, behavior, and maternal well-being. *Pediatrics*, 111(3), e203-e207.
- Landolt, Meier, Burgess, Finelli, Cattelin, Achermann, & Borbély. (1999). Serotonin-2 receptors and human sleep: Effect of a selective antagonist on eeg power spectra. *Neuropsychopharmacology*, 21(3), 455-466.
- Laplante, Brunet, Schmitz, Ciampi, & King. (2008). Project ice storm: Prenatal maternal stress affects cognitive and linguistic functioning in 5½-year-old children. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47(9), 1063-1072.
- Lavigne, Arend, Rosenbaum, Smith, Weissbluth, Binns, & Christoffel. (1999). Sleep and behavior problems among preschoolers. *Journal of Developmental & Behavioral Pediatrics*, 20(3), 164-169.
- Lee, & Bates. (1985). Mother-child interaction at age two years and perceived difficult temperament. *Child Development*, 56(5), 1314-1325.
- Lee, & Gay. (2004). Sleep in late pregnancy predicts length of labor and type of delivery. *American Journal of Obstetrics and Gynecology*, 191(6), 2041-2046.
- Lee, & Rosen (Eds.). (2012). *Sleep and human development*. Oxford: Oxford University Press.
- Lengua. (2008). Anxiousness, frustration, and effortful control as moderators of the relation between parenting and adjustment in middle-childhood. *Social Development*, 17(3), 554-577.
- Leonardo, & Hen. (2006). Genetics of affective and anxiety disorders. *Annu. Rev. Psychol.*, 57, 117-137.
- Lesch. (2001). Serotonergic gene expression and depression: Implications for developing novel antidepressants. *Journal of Affective Disorders*, 62(1-2), 57-76.
- Lesch, Bengel, Heils, Sabol, Greenberg, Petri, . . . Murphy. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, 274(5292), 1527.
- Leve, Kim, & Pears. (2005). Childhood temperament and family environment as predictors of internalizing and externalizing trajectories from ages 5 to 17. *Journal of Abnormal Child Psychology*, 33(5), 505-520.
- Lewis, Pelosi, Araya, & Dunn. (1992). Measuring psychiatric disorder in the community: A standardized assessment for use by lay interviewers. *Psychological Medicine*, 22(02), 465-486.
- Lin, & Su. (2007). A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *Journal of Clinical Psychiatry*, 68(7), 1056-1061.
- Lindgren. (2001). Relationships among maternal-fetal attachment, prenatal depression, and health practices in pregnancy. *Research in Nursing & Health*, 24(3), 203-217.
- Linkowski. (1999). Eeg sleep patterns in twins. *Journal of sleep research*, 8(1), 11-13.
- Linkowski, Kerkhofs, Hauspie, & Mendlewicz. (1991). Genetic determinants of eeg sleep: A study in twins living apart. *Electroencephalography and clinical Neurophysiology*, 79(2), 114-118.

- Linkowski, Kerkhofs, Hauspie, Susanne, & Mendlewicz. (1989). Eeg sleep patterns in man: A twin study. *Electroencephalography and clinical Neurophysiology*, 73(4), 279-284.
- Linn, McClure, Monaghan, Blulun, Watson, & Roth. (2007). Association of serotonin transporter (5htt) gene polymorphism with amount of slow-wave sleep in human subjects. *Sleep*, 30, A365.
- Little, Higgins, Ioannidis, Moher, Gagnon, Von Elm, . . . Grimshaw. (2009). Strengthening the reporting of genetic association studies (strega)—an extension of the strobe statement. *European journal of clinical investigation*, 39(4), 247-266.
- Lockley, & Foster. (2012). *Sleep: A very short introduction* (Vol. 295): Oxford University Press.
- Loutzenhiser, & Seigny. (2008). Infant sleep and the quality of family life for first-time parents of three-month-old infants. *Fathering: A Journal of Theory, Research, and Practice about Men as Fathers*, 6(1), 2-19.
- Luijk, Roisman, Haltigan, Tiemeier, Booth-LaForce, van IJendoorn, . . . Hofman. (2011). Dopaminergic, serotonergic, and oxytonergic candidate genes associated with infant attachment security and disorganization? In search of main and interaction effects. *Journal of Child Psychology and Psychiatry*.
- Lund, Reider, Whiting, & Prichard. (2010). Sleep patterns and predictors of disturbed sleep in a large population of college students. *Journal of Adolescent Health*, 46(2), 124-132.
- Lundy, Jones, Field, Nearing, Davalos, Pietro, . . . Kuhn. (1999a). Prenatal depression effects on neonates. *Infant Behavior and Development*, 22(1), 119-129.
- Lundy, Jones, Field, Nearing, Davalos, Pietro, . . . Kuhn. (1999b). Prepartum depression effects on neonates. *Infant Behavior and Development*, 22, 121-137.
- Luoma, Tamminen, & Koivisto. (2004). Fathers' and mothers' perceptions of their child and maternal depressive symptoms. *Nord J Psychiatry*, 58, 205-211.
- Maccari, Darnaudery, Morley-Fletcher, Zuena, Cinque, & Van Reeth. (2003). Prenatal stress and long-term consequences: Implications of glucocorticoid hormones. *Neuroscience and Biobehavioral Reviews*, 27(1), 119-128.
- Mairesse, Lesage, Breton, Bréant, Hahn, Darnaudéry, . . . Vieau. (2007). Maternal stress alters endocrine function of the feto-placental unit in rats. *American Journal of Physiology-Endocrinology And Metabolism*, 292(6), E1526-E1533.
- Makrides, Gibson, McPhee, Yell, Quinlivan, & Ryan. (2011). Effect of dha supplementation during pregnancy on maternal depression and neurodevelopment of young children: A randomized controlled trial. *Obstetrical & Gynecological Survey*, 66(2), 79.
- Manber, Schnyer, Allen, Rush, & Blasey. (2004). Acupuncture: A promising treatment for depression during pregnancy. *Journal of affective disorders*, 83(1), 89-95.
- Manber, Schnyer, Lyell, Chambers, Caughey, Druzin, . . . Huang. (2010). Acupuncture for depression during pregnancy: A randomized controlled trial. *Obstetrics & Gynecology*, 115(3), 511.
- Mathers, Fat, & Boerma. (2008). *The global burden of disease: 2004 update*: World Health Organization.
- Matthey, Barnett, Kavanagh, & Howie. (2001). Validation of the edinburgh postnatal depression scale for men, and comparison of item endorsement with their partners. *Journal of Affective Disorders*, 64(2-3), 175-184.
- McCarren, Goldberg, Ramakrishnan, & Fabsitz. (1994). Insomnia in vietnam era veteran twins: Influence of genes and combat experience. *Sleep*, 17(5), 456.

- McGinty, & Serman. (1968). Sleep suppression after basal forebrain lesions in the cat. *Science*, 160(3833), 1253.
- McGrath, Records, & Rice. (2008). Maternal depression and infant temperament characteristics. *Infant Behavior and Development*, 31(1), 71-80.
- McGregor. (2008). *A physician-based cognitive behavioural intervention for depressed pregnant women in primary care: A pilot study.*, University of Toronto, Canada. Retrieved from <http://search.proquest.com/docview/304368576?accountid=13042> Available from ProQuest Dissertations and Theses (304368576)
- Meltzer, Montgomery-Downs, Insana, & Walsh. (2012). Use of actigraphy for assessment in pediatric sleep research. *Sleep Medicine Reviews*.
- Milan, Snow, & Belay. (2007). The context of preschool children's sleep: Racial/ethnic differences in sleep locations, routines, and concerns. *Journal of Family Psychology*, 21(1), 20.
- Milgrom, Westley, & McCloud. (1995). Do infants of depressed mothers cry more than other infants? *Journal of paediatrics and child health*, 31(3), 218-221.
- Mindell, & Owens. (2003). Sleep problems in pediatric practice: Clinical issues for the pediatric nurse practitioner. *Journal of Pediatric Health Care*, 17(6), 324-331.
- Mirmiran. (1995). The function of fetal/neonatal rapid eye movement sleep. *Behavioural brain research*, 69(1), 13-22.
- Mirmiran, Maas, & Ariagno. (2003). Development of fetal and neonatal sleep and circadian rhythms. *Sleep Medicine Reviews*, 7(4), 321-344.
- Mirmiran, & Someren. (1993). The importance of rem sleep for brain maturation. *Journal of Sleep Research*, 2(4), 188-192.
- Mirmiran, Van de Poll, Corner, Van Oyen, & Bour. (1981). Suppression of active sleep by chronic treatment with chlorimipramine during early postnatal development: Effects upon adult sleep and behavior in the rat. *Brain research*, 204(1), 129-146.
- Monaca, Boutrel, Hen, Hamon, & Adrien. (2003). 5-HT_{1A/1B} receptor-mediated effects of the selective serotonin reuptake inhibitor, citalopram, on sleep: Studies in 5-HT_{1A} and 5-HT_{1B} knockout mice. *Neuropsychopharmacology*, 28(5), 850-856.
- Monk, Reynolds, Kupfer, Buysse, Coble, Hayes, . . . Ritenour. (1994). The pittsburgh sleep diary. *Journal of Sleep Research*, 3(2), 111-120. doi: 10.1111/j.1365-2869.1994.tb00114.x
- Monk, Spicer, & Champagne. (2012). Linking prenatal maternal adversity to developmental outcomes in infants: The role of epigenetic pathways. *Development and psychopathology*, 24(04), 1361-1376.
- Monroe, & Simons. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological bulletin*, 110(3), 406.
- Monti. (2011). Serotonin control of sleep-wake behavior. *Sleep Medicine Reviews*.
- Morgan, Shaw, & Olino. (2012). Differential susceptibility effects: The interaction of negative emotionality and sibling relationship quality on childhood internalizing problems and social skills. *Journal of Abnormal Child Psychology*, 1-15.
- Morrell. (1999). The role of maternal cognitions in infant sleep problems as assessed by a new instrument, the maternal cognitions about infant sleep questionnaire. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, 40(02), 247-258.

- Morrell, & Murray. (2003). Parenting and the development of conduct disorder and hyperactive symptoms in childhood: A prospective longitudinal study from 2 months to 8 years. *Journal of Child Psychology and Psychiatry*, 44(4), 489-508.
- Morrison, McGEE, & Stanton. (1992). Sleep problems in adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry*, 31(1), 94-99.
- Munafò, Durrant, Lewis, & Flint. (2009). Gene× environment interactions at the serotonin transporter locus. *Biological psychiatry*, 65(3), 211-219.
- Munafò MR, Durrant C, Lewis G, & J. (2009). Gene x environment interactions at the serotonin transporter locus. *Biol Psychiatry*, 65(3), 211-219.
- Murray. (1992). The impact of postnatal depression on infant development. *Journal of Child Psychology and Psychiatry*, 33(3), 543-561.
- Murray, & Carothers. (1990). The validation of the edinburgh post-natal depression scale on a community sample. *British Journal of Psychiatry*, 157, 288-290.
- Murray, & Cox. (1990). Screening for depression during pregnancy with the edinburgh postnatal depression scale *J. Reprod. Infant Psychol. Journal of Family Psychology*, 8(99-107).
- Murray, Creswell, & Cooper. (2009). The development of anxiety disorders in childhood: An integrative review. *Psychological Medicine*, 39(9), 1413.
- Murrough, & Charney. (2011). The serotonin transporter and emotionality: Risk, resilience, and new therapeutic opportunities. *Biological psychiatry*, 69(6), 510-512.
- Nevarez, Rifas-Shiman, Kleinman, Gillman, & Taveras. (2010). Associations of early life risk factors with infant sleep duration. *Academic pediatrics*, 10(3), 187-193.
- NICE. (2007). *Antenatal and postnatal mental health*. London: National Institute for Health and Care Excellence.
- Nixon, Thompson, Han, Becroft, Clark, Robinson, . . . Mitchell. (2008). Short sleep duration in middle childhood: Risk factors and consequences. *Sleep*, 31(1), 71.
- Novosad, Freudigman, & Thoman. (1999). Sleep patterns in newborns and temperament at eight months: A preliminary study. *Journal of developmental and behavioral pediatrics*.
- O'Connor. (2007). Prenatal mood disturbance predicts sleep problems in infancy and toddlerhood. *Early Human Development*, 83(7), 451.
- O'Connor, Bergman, Sarkar, & Glover. (2012). Prenatal cortisol exposure predicts infant cortisol response to acute stress. *Developmental psychobiology*.
- O'Connor, Heron, Golding, Beveridge, & Glover. (2002). Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years: Report from the avon longitudinal study of parents and children. *The British journal of psychiatry*, 180(6), 502.
- O'Connor, Heron, Golding, Glover, & ALSPAC. (2003). Maternal antenatal anxiety and behavioural/emotional problems in children: A test of a programming hypothesis. *J Child Psychol Psychiatry*, Oct;44(7), 1025-1036.
- O'Hara, & Swain. (1996). Rates and risk of postpartum depression: A meta-analysis. *International Review of Psychiatry*, 8(1), 37-54. doi:10.3109/09540269609037816
- O'Mahen, Flynn, & Nolen-Hoeksema. (2010). Rumination and interpersonal functioning in perinatal depression. *Journal of Social and Clinical Psychology*, 29(6), 646-667.
- O'Mahen, Himle, Fedock, Henshaw, & Flynn. (2013). A pilot randomized controlled trial of cognitive behavioral therapy for perinatal depression adapted for women with low incomes. *Depression and anxiety*.

- O'Connor, Ben-Shlomo, Heron, Golding, Adams, & Glover. (2005). Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biological psychiatry*, 58(3), 211-217.
- O'Donnell, Bugge Jensen, Freeman, Khalife, O'Connor, & Glover. (2012). Maternal prenatal anxiety and downregulation of placental 11 β -hsd2. *Psychoneuroendocrinology*, 37(6), 818-826.
- O'Donnell, O'Connor, & Glover. (2009). Prenatal stress and neurodevelopment of the child: Focus on the hpa axis and role of the placenta. *Developmental neuroscience*, 31(4), 285-292.
- Oberlander, Papsdorf, Brain, Misri, Ross, & Grunau. (2010). Prenatal effects of selective serotonin reuptake inhibitor antidepressants, serotonin transporter promoter genotype (slc6a4), and maternal mood on child behavior at 3 years of age. *Archives of Pediatrics and Adolescent Medicine*, 164(5), 444.
- Oberndorfer, Saletu-Zyhlarz, & Saletu. (2000). Effects of selective serotonin reuptake inhibitors on objective and subjective sleep quality. *Neuropsychobiology*, 42(2), 69-81.
- Obradović, Bush, Stamperdahl, Adler, & Boyce. (2010). Biological sensitivity to context: The interactive effects of stress reactivity and family adversity on socioemotional behavior and school readiness. *Child Development*, 81(1), 270-289.
- Okun, Coussons-Read, & Hall. (2009). Disturbed sleep is associated with increased c-reactive protein in young women. *Brain, behavior, and immunity*, 23(3), 351-354.
- Oren, Wisner, Spinelli, Epperson, Peindl, Terman, & Terman. (2002). An open trial of morning light therapy for treatment of antepartum depression. *American Journal of Psychiatry*, 159(4), 666-669.
- Ortiz, Manber, Schnyer, Lyell, Chambers, Caughey, . . . Gress. (2010). Acupuncture for depression during pregnancy: A randomized controlled trial. *Deutsche Zeitschrift für Akupunktur*, 53(2), 43-45.
- Osborn, Harris, Reading, & Prather. (1990). Outcome of pregnancies experienced during residency. *The Journal of family practice*, 31(6), 618-622.
- Owens, Spirito, McGUINN, & Nobile. (2000). Sleep habits and sleep disturbance in elementary school-aged children. *Journal of Developmental & Behavioral Pediatrics*, 21(1), 27-36.
- Owens, & Witmans. (2004). Sleep problems. *Current problems in pediatric and adolescent health care*, 34(4), 154.
- Parmelee, Wenner, Akiyama, Schultz, & Stern. (1967). Sleep states in premature infants. *Developmental Medicine & Child Neurology*, 9(1), 70-77.
- Partinen. (1983). Genetic and environmental determination of human sleep. *Sleep: Journal of Sleep Research & Sleep Medicine*.
- Pawlby, Hay, Sharp, Waters, & O'Keane V. (2008). Antenatal depression predicts depression in adolescent offspring: Prospective longitudinal community-based study. *J Affect Disord*, 3[Epub ahead of print].
- Pawlby, Hay, Sharp, Waters, & Pariante. (2011). Antenatal depression and offspring psychopathology: The influence of childhood maltreatment. *The British Journal of Psychiatry*, 199(2), 106-112.
- Pawlby, Sharp, Hay, & O'Keane. (2008). Antenatal depression predicts depression in adolescent offspring: Prospective longitudinal community-based study. *Journal of Affective Disorders*, 107(1), 54.

- Pearson, Cooper, Penton-Voak, Lightman, & Evans. (2010). Depressive symptoms in early pregnancy disrupt attentional processing of infant emotion. *Psychol Med*, 40(4), 621-631.
- Pearson, Fernyhough, Bentall, Evans, Heron, Joinson, . . . Lewis. (2013). Association between maternal depressogenic cognitive style during pregnancy and offspring cognitive style 18 years later. *American Journal of Psychiatry*.
- Pearson, Melotti, Heron, Joinson, Stein, Ramchandani, & Evans. (2012). Disruption to the development of maternal responsiveness? The impact of prenatal depression on mother–infant interactions. *Infant Behavior and Development*, 35(4), 613-626.
- Peirano, Algarín, & Uauy. (2003). Sleep-wake states and their regulatory mechanisms throughout early human development. *The Journal of pediatrics*, 143(4), 70-79.
- Perlis, Mischoulon, Smoller, Wan, Lamon-Fava, Lin, . . . Fava. (2003). Serotonin transporter polymorphisms and adverse effects with fluoxetine treatment. *Biological psychiatry*, 54(9), 879-883.
- Pesonen, Räikkönen, Strandberg, & Järvenpää. (2005). Continuity of maternal stress from the pre-to the postnatal period: Associations with infant's positive, negative and overall temperamental reactivity. *Infant Behavior and Development*, 28(1), 36-47.
- Piteo, Roberts, Nettelbeck, Burns, Lushington, Martin, & Kennedy. (2012). Postnatal depression mediates the relationship between infant and maternal sleep disruption and family dysfunction. *Early human development*.
- Pitzer, Jennen-Steinmetz, Esser, Schmidt, & Laucht. (2011). Differential susceptibility to environmental influences: The role of early temperament and parenting in the development of externalizing problems. *Comprehensive Psychiatry*.
- Plomin, DeFries, McClearn, & McGuffin. (2008). *Behavioral genetics*: Worth Publishers.
- Pluess, & Belsky. (2009). Differential susceptibility to rearing experience: The case of childcare. *Journal of Child Psychology and Psychiatry*, 50(4), 396-404.
- Pluess, & Belsky. (2010). Differential susceptibility to parenting and quality child care. *Developmental Psychology*, 46(2), 379.
- Pluess, & Belsky. (2011). Differential susceptibility to maternal sensitivity. In Winders Davis D. & Cynthia Logsdon M. (Eds.), *Maternal sensitivity: A critical review for practitioners* (pp. 95-107). Hauppauge, NY: Nova Science Publishers, Inc.
- Pluess, Bolten, Pirke, & Hellhammer. (2010). Maternal trait anxiety, emotional distress, and salivary cortisol in pregnancy. *Biological psychology*, 83(3), 169-175.
- Pluess, Velders, Belsky, van IJzendoorn, Bakermans-Kranenburg, Jaddoe, . . . Tiemeier. (2010). Serotonin transporter polymorphism moderates effects of prenatal maternal anxiety on infant negative emotionality. *Biological psychiatry*, 34(6), 1070-1074.
- Ponirakis, Susman, & Stifter. (1998). Negative emotionality and cortisol during adolescent pregnancy and its effects on infant health and autonomic nervous system reactivity. *Developmental psychobiology*, 33(2), 163-174.
- Prince, Stewart, Ford, & Hotopf. (2003). *Practical psychiatric epidemiology*. Oxford: Oxford University Press.
- Rahman, Malik, Sikander, Roberts, & Creed. (2008). Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural pakistan: A cluster-randomised controlled trial. *The Lancet*, 372(9642), 902-909.

- Ramchandani, Stein, O'Connor, Heron, Murray, & Evans. (2008). Depression in men in the postnatal period and later child psychopathology: A population cohort study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47(4), 390.
- Ramchandani, van IJzendoorn, & Bakermans-Kranenburg. (2010). Differential susceptibility to fathers' care and involvement: The moderating effect of infant reactivity. *Family Science*, 1(2), 93-101.
- Rees, Austin, & Parker. (2008). Omega-3 fatty acids as a treatment for perinatal depression: Randomized double-blind placebo-controlled trial. *Australasian Psychiatry*, 42(3), 199-205.
- Regier, Rae, Narrow, Kaelber, & Schatzberg. (1998). Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. *The British Journal of Psychiatry*.
- Reid, Hong, & Wade. (2009). The relation between common sleep problems and emotional and behavioral problems among 2-and 3-year-olds in the context of known risk factors for psychopathology. *Journal of sleep research*, 18(1), 49-59.
- Rice, Harold, Boivin, Hay, van den Bree, & Thapar. (2009). Disentangling prenatal and inherited influences in humans with an experimental design. *Proceedings of the National Academy of Sciences*, 106(7), 2464-2467.
- Richter, Bittner, Petrowski, Junge-Hoffmeister, Bergmann, Joraschky, & Weidner. (2012). Effects of an early intervention on perceived stress and diurnal cortisol in pregnant women with elevated stress, anxiety, and depressive symptomatology. *Journal of Psychosomatic Obstetrics & Gynecology*, 33(4), 162-170.
- Richters. (1992). Depressed mothers as informants about their children: A critical review of the evidence for distortion. *Psychological bulletin*, 112(3), 485.
- Risch, Herrell, Lehner, Liang, Eaves, Hoh, . . . Merikangas. (2009). Interaction between the serotonin transporter gene (5-httlpr), stressful life events, and risk of depression. *JAMA: the journal of the American Medical Association*, 301(23), 2462-2471.
- Rodriguez, & Bohlin. (2005). Are maternal smoking and stress during pregnancy related to adhd symptoms in children? *Journal of Child Psychology and Psychiatry*, 46(3), 246-254.
- Rodriguez, Gaunt, & Day. (2009). Hardy-weinberg equilibrium testing of biological ascertainment for mendelian randomization studies. *American journal of epidemiology*, 169(4), 505-514.
- Roenneberg, & Mellow. (2005). Circadian clocks the fall and rise of physiology. *Nat Rev Mol Cell Biol*, 6(12), 965-971.
- Rogers, Caruso, & Aldrich. (1993). Reliability of sleep diaries for assessment of sleep/wake patterns. *Nursing Research; Nursing Research*.
- Rothbart. (1981). Measurement of temperament in infancy. *Child Development*, 52, 569-578.
- Rothbart, & Bates. (2006). Temperament. In Damon, Lerner & Eisenberg (Eds.), *Handbook of child psychology, social, emotional, and personality development* (Vol. 3, pp. 105-163). New York: Wiley.
- Rothenberg, Moehler, Reck, & Resch. (2010). Prenatal stress: Course and interrelation of emotional and physiological stress measures. *Psychopathology*, 44(1), 60-67.

- Rutter. (2007). Proceeding from observed correlation to causal inference: The use of natural experiments. *Perspectives on Psychological Science*, 2(4), 377-395.
- Ryo, Nishihara, Matsumoto, & Kamata. (2012). A new method for long-term home monitoring of fetal movement by pregnant women themselves. *Medical engineering & physics*, 34(5), 566-572.
- Sadeh. (2004a). A brief screening questionnaire for infant sleep problems: Validation and findings for an internet sample. *Pediatrics*, 113(6), e570-e577.
- Sadeh. (2004b). A brief screening questionnaire for infant sleep problems: Validation and findings for an internet sample. *Pediatrics*, 113(6), e570.
- Sadeh. (2007). Consequences of sleep loss or sleep disruption in children. *Sleep Medicine Clinics*, 2(3), 513-520.
- Sadeh, Flint-Ofir, Tirosh, & Tikotzky. (2007). Infant sleep and parental sleep-related cognitions. *Journal of family psychology*, 21(1), 74.
- Sadeh, Gruber, & Raviv. (2003a). The effects of sleep restriction and extension on school-age children: What a difference an hour makes. *Child development*, 74(2), 444-455.
- Sadeh, Gruber, & Raviv. (2003b). Sleep, neurobehavioral functioning, and behavior problems in school-age children. *Child development*, 73(2), 405-417.
- Sadeh, Lavie, Scher, Tirosh, & Epstein. (1991). Actigraphic home-monitoring sleep-disturbed and control infants and young children: A new method for pediatric assessment of sleep-wake patterns. *Pediatrics*, 87(4), 494-499.
- Sadeh, Mindell, Luedtke, & Wiegand. (2009). Sleep and sleep ecology in the first 3 years: A web-based study. *Journal of Sleep Research*, 18(1), 60-73.
- Sadeh, Tikotzky, & Scher. (2010). Parenting and infant sleep. *Sleep medicine reviews*, 14(2), 89-96.
- Sahota. (2003). Sleep disorders in pregnancy. *Current opinion in pulmonary medicine*, 9(6), 477.
- Sallanon, Janin, Buda, & Jouvet. (1983). Serotonergic mechanisms and sleep rebound. *Brain research*, 268(1), 95-104.
- Sandman, Glynn, Schetter, Wadhwa, Garite, Chicz-DeMet, & Hobel. (2006). Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental corticotropin releasing hormone (crh): Priming the placental clock. *Peptides*, 27(6), 1457-1463.
- Sandman, Wadhwa, Chicz-DeMet, Porto, & Garite. (1999). Maternal corticotropin-releasing hormone and habituation in the human fetus. *Developmental Psychobiology*, 34(3), 163-173.
- Sandman, Wadhwa, Glynn, Chicz-Demet, Porto, & Garite. (1999). Corticotrophin-releasing hormone and fetal responses in human pregnancy. *Annals of the New York Academy of Sciences*, 897(1), 66-75.
- Schaefer. (1990a). Night waking and temperament in early childhood. *Psychological Reports*, 67(1), 192-194.
- Schaefer. (1990b). Night waking and temperament in early childhood. *Psychological Reports*, 67(1), 192-194.
- Scher. (2005). Infant sleep at 10 months of age as a window to cognitive development. *Early Human Development*, 81(3), 289-292.
- Scher, Epstein, Sadeh, Tirosh, & Lavie. (1992). Toddlers' sleep and temperament: Reporting bias or a valid link? A research note. *Journal of Child Psychology and Psychiatry*, 33(7), 1249-1254.

- Scher, Tirosh, & Lavie. (1998). Relationship between sleep and temperament revisited: Evidence for 12-month-olds: A research note. *Journal of Child Psychology and Psychiatry*, 39(5), 785-788.
- Schlotz, & Phillips. (2009). Fetal origins of mental health: Evidence and mechanisms. *Brain, behavior, and immunity*, 23(7), 905-916.
- Schneider, Moore, Kraemer, Roberts, & DeJesus. (2002). The impact of prenatal stress, fetal alcohol exposure, or both on development: Perspectives from a primate model. *Psychoneuroendocrinology*, 27(1), 285-298.
- Serretti, Benedetti, Mandelli, Lorenzi, Pirovano, Colombo, & Smeraldi. (2003). Genetic dissection of psychopathological symptoms: Insomnia in mood disorders and clock gene polymorphism. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 121(1), 35-38.
- Serretti, Kato, De Ronchi, & Kinoshita. (2006). Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Molecular psychiatry*, 12(3), 247-257.
- Simard, Lara-Carrasco, Paquette, & Nielsen. (2011). Breastfeeding, maternal depressive mood and room sharing as predictors of sleep fragmentation in 12-week-old infants: A longitudinal study. *Early Child Development and Care*, 181(8), 1063-1077.
- Simola, Liukkonen, Pitkäranta, Pirinen, & Aronen. (2012). Psychosocial and somatic outcomes of sleep problems in children: A 4-year follow-up study. *Child: Care, Health and Development*.
- Skouteris, Germano, Wertheim, Paxton, & Milgrom. (2008). Sleep quality and depression during pregnancy: A prospective study. *Journal of sleep research*, 17(2), 217-220.
- Smaldone, Honig, & Byrne. (2009). Does assessing sleep inadequacy across its continuum inform associations with child and family health? *Journal of Pediatric Health Care*, 23(6), 394-404.
- Smeekeens, Riksen-Walraven, & van Bakel. (2007). Multiple determinants of externalizing behavior in 5-year-olds: A longitudinal model. *Journal of Abnormal Child Psychology*, 35(3), 347-361.
- Smeraldi, Zanardi, Benedetti, Di Bella, Perez, & Catalano. (1998). Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. *Molecular psychiatry*, 3(6), 508.
- So, Buckley, Adamson, & Horne. (2005). Actigraphy correctly predicts sleep behavior in infants who are younger than six months, when compared with polysomnography. *Pediatric research*, 58(4), 761-765.
- Sodhi, & Sanders-Bush. (2004). Serotonin and brain development. *International review of neurobiology*, 59, 111-174.
- Someren, Swaab, Christopher, Cohen, McCall, & Rosenquist. (1999). Bright lights therapy: Improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. *Chronobiology international*, 16(4), 505-518.
- Spielberger, Gorsuch, & Edward. (1970). *Stai manual for the state-trait anxiety inventory ("self-evaluation questionnaire")*: Consulting Psychologists Press.
- Spinelli, & Endicott. (2003). Controlled clinical trial of interpersonal psychotherapy versus parenting education program for depressed pregnant women. *American Journal of Psychiatry*, 160(3), 555-562.

- Spinelli, & Endicott. (2005). Ntepartum study on use of interpersonal psychotherapy at 3 new york city site Retrieved 5 Novemeber 2012, from <http://clinicaltrials.gov/ct/show/NCT00251043>
- Spruyt, Aitken, So, Charlton, Adamson, & Horne. (2008). Relationship between sleep/wake patterns, temperament and overall development in term infants over the first year of life. *Early Human Development*, 84(5), 289-296.
- Spruyt, Gozal, Dayyat, Roman, & Molfese. (2010). Sleep assessments in healthy school-aged children using actigraphy: Concordance with polysomnography. *Journal of sleep research*, 20(1pt2), 223-232.
- Stein, Craske, Lehtonen, Harvey, Savage-McGlynn, Davies, . . . Counsell. (2012). Maternal cognitions and mother-infant interaction in postnatal depression and generalized anxiety disorder. *J Abnorm Psychol* (Epub ahead of print).
- Stoléro, Nottelmann, Belmont, & Ronsaville. (2006). Sleep problems in children of affectively ill mothers. *Journal of Child Psychology and Psychiatry*, 38(7), 831-841.
- Streissguth, Sampson, Olson, Bookstein, Barr, Scott, . . . Mirsky. (1994). Maternal drinking during pregnancy: Attention and short-term memory in 14-year-old offspring—a longitudinal prospective study. *Alcoholism: Clinical and Experimental Research*, 18(1), 202-218.
- Su, Huang, Chiu, Huang, Huang, Chang, & Pariante. (2008). Omega-3 fatty acids for major depressive disorder during pregnancy: Results from a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry*, 69(4), 644.
- Suomi. (1997). Early determinants of behaviour: Evidence from primate studies. *British Medical Bulletin*, 53(1), 170-184.
- Swartjes, Van Geijn, Mantel, Van Woerden, & Schoemaker. (1990). Coincidence of behavioural state parameters in the human fetus at three gestational ages. *Early human development*, 23(2), 75-83.
- Tafti, & Franken. (2002). Invited review: Genetic dissection of sleep. *Journal of Applied Physiology*, 92(3), 1339-1347.
- Talge, Neal, & Glover. (2007). Antenatal maternal stress and long-term effects on child neurodevelopment: How and why? *J Child Psychol Psychiatry*, 48(3-4), 245-261.
- Taylor, Way, Welch, Hilmert, Lehman, & Eisenberger. (2006). Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. *Biological psychiatry*, 60(7), 671-676.
- Testa, Quigley, & Eiden. (2003). The effects of prenatal alcohol exposure on infant mental development: A meta-analytical review. *Alcohol and Alcoholism*, 38(4), 295-304.
- Teti, & Crosby. (2012). Maternal depressive symptoms, dysfunctional cognitions, and infant night waking: The role of maternal nighttime behavior. *Child development*.
- Thomas. (2010). Gene–environment-wide association studies: Emerging approaches. *Nature Reviews Genetics*, 11(4), 259-272.
- Tikotzky, Chambers, Kent, Gaylor, & Manber. (2012). Postpartum maternal sleep and mothers' perceptions of their attachment relationship with the infant among women with a history of depression during pregnancy. *International Journal of Behavioral Development*.

- Tikotzky, & Sadeh. (2009). Maternal sleep-related cognitions and infant sleep: A longitudinal study from pregnancy through the 1st year. *Child development*, 80(3), 860-874.
- Toh, Jones, He, Eide, Hinz, Virshup, . . . Fu. (2001). An hper2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science Signalling*, 291(5506), 1040.
- Touchette, Petit, Paquet, Boivin, Japel, Tremblay, & Montplaisir. (2005). Factors associated with fragmented sleep at night across early childhood. *Archives of pediatrics & adolescent medicine*, 159(3), 242.
- Touchette, Petit, Séguin, Boivin, Tremblay, & Montplaisir. (2007). Associations between sleep duration patterns and behavioral/cognitive functioning at school entry. *Sleep*, 30(9), 1213.
- Ursache, Blair, Stifter, & Voegtline. (2012). Emotional reactivity and regulation in infancy interact to predict executive functioning in early childhood.
- Van Aken, Junger, Verhoeven, Van Aken, & Deković. (2007). The interactive effects of temperament and maternal parenting on toddlers' externalizing behaviours. *Infant and Child Development*, 16(5), 553-572.
- Van De Water, Holmes, & Hurley. (2011). Objective measurements of sleep for non-laboratory settings as alternatives to polysomnography—a systematic review. *Journal of Sleep Research*, 20(1pt2), 183-200.
- Van den Bergh. (2007). Antenatal maternal anxiety is related to hpa-axis dysregulation and self-reported depressive symptoms in adolescence: A prospective study on the fetal origins of depressed mood. *Neuropsychopharmacology*, 33(3), 536.
- Van den Bergh, & Marcoen. (2004). High antenatal maternal anxiety is related to adhd symptoms, externalizing problems, and anxiety in 8-and 9-year-olds. *Child Development*, 75(4), 1085.
- Van den Bergh, Mulder, Mennes, & Glover. (2005). Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: Links and possible mechanisms. A review. *Neuroscience & Biobehavioral Reviews*, 29(2), 237-258.
- van Ijzendoorn, Belsky, & Bakermans-Kranenburg. (2012). Serotonin transporter genotype 5httlpr as a marker of differential susceptibility; a meta-analysis of child and adolescent gene-by-environment studies. *Translational psychiatry*, 2(8), e147.
- Velderman, Bakermans-Kranenburg, Juffer, & van IJzendoorn. (2006). Effects of attachment-based interventions on maternal sensitivity and infant attachment: Differential susceptibility of highly reactive infants. *Journal of Family Psychology*, 20(2), 266.
- Vieten, & Astin. (2008). Effects of a mindfulness-based intervention during pregnancy on prenatal stress and mood: Results of a pilot study. *Archives of women's mental health*, 11(1), 67-74.
- Visser, Poelman-Weeshes, Cohen, & Bekedam. (1987). Fetal behavior at 30 to 32 weeks of gestation. *Pediatric research*, 22(6), 655-658.
- Volling, & Feagans. (1995). Infant day care and children's social competence. *Infant Behavior and Development*, 18(2), 177-188.
- Vreeburg, Hartman, Hoogendijk, van Dyck, Zitman, Ormel, & Penninx. (2010). Parental history of depression or anxiety and the cortisol awakening response. *The British Journal of Psychiatry*, 197(3), 180-185.
- Wadhwa, Garite, Porto, Glynn, Chicz-DeMet, Dunkel-Schetter, & Sandman. (2004). Placental corticotropin-releasing hormone (crh), spontaneous preterm birth, and

- fetal growth restriction: A prospective investigation. *American journal of obstetrics and gynecology*, 191(4), 1063-1069.
- Wadhwa, Sandman, Chicz-Demet, & Porto. (1997). Placental crh modulates maternal pituitary-adrenal function in human pregnancy. *Annals of the New York Academy of Sciences*, 814(1), 276-281.
- Wadhwa, Sandman, & Garite. (2001). The neurobiology of stress in human pregnancy: Implications for prematurity and development of the fetal central nervous system. *Progress in Brain Research*, 133, 131-142.
- Ward, Zucchi, Robbins, Falkenberg, Olson, Benzies, & Metz. (2013). Transgenerational programming of maternal behaviour by prenatal stress. *BMC Pregnancy and Childbirth*, 13(Suppl 1), S9.
- Watson, Buchwald, Vitiello, Noonan, & Goldberg. (2010). A twin study of sleep duration and body mass index. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*, 6(1), 11.
- Watson, Goldberg, Arguelles, & Buchwald. (2006). Genetic and environmental influences on insomnia, daytime sleepiness, and obesity in twins. *SLEEP-NEW YORK THEN WESTCHESTER-*, 29(5), 645.
- Weaver, Cervoni, Champagne, D'Alessio, Sharma, Seckl, . . . Meaney. (2004). Epigenetic programming by maternal behavior. *Nature neuroscience*, 7(8), 847-854.
- Weinberg. (1993). Toward a clearer definition of confounding. *American Journal of Epidemiology*, 137(1), 1-8.
- Weinstock. (1997). Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? *Neuroscience & Biobehavioral Reviews*, 21(1), 1-10.
- Weinstock. (2001). Alterations induced by gestational stress in brain morphology and behaviour of the offspring. *Progress in Neurobiology*, 65(5), 427-451.
- Weinstock. (2005). The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain, behavior, and immunity*, 19(4), 296-308.
- Weinstock. (2008). The long-term behavioural consequences of prenatal stress. *Neuroscience & Biobehavioral Reviews*, 32(6), 1073-1086.
- Weissbluth. (1983). Sleep duration and infant temperament. *Annual progress in child psychiatry and child development*, 383.
- Werner, Myers, Fifer, Cheng, Fang, Allen, & Monk. (2007). Prenatal predictors of infant temperament. *Developmental psychobiology*, 49(5), 474-484.
- WHO. (2004, 22-24 January 2004). World health organization technical meeting on sleep and health, January 2009, from http://www.euro.who.int/document/E84683_1.pdf
- Wiggs. (2007). Are children getting enough sleep? Implications for parents. *Sociological Research Online*, 12(5), 13.
- Wiggs, Montgomery, & Stores. (2005). Actigraphic and parent reports of sleep patterns and sleep disorders in children with subtypes of attention-deficit hyperactivity disorder. *SLEEP-NEW YORK THEN WESTCHESTER-*, 28(11), 1437.
- Wirz-Justice, Bader, Frisch, Stieglitz, Alder, Bitzer, . . . Terman. (2011). A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. *The Journal of clinical psychiatry*, 72(7), 986-993.
- Wisor, Wurts, Hall, Lesch, Murphy, Uhl, & Edgar. (2003). Altered rapid eye movement sleep timing in serotonin transporter knockout mice. *Neuroreport*, 14(2), 233.

- Wolfson, Crowley, Anwer, & Bassett. (2003). Changes in sleep patterns and depressive symptoms in first-time mothers: Last trimester to 1-year postpartum. *Behavioral Sleep Medicine*, 1(1), 54-67.
- Wulff, Dedek, & Siegmund. (2001). Circadian and ultradian time patterns in human behavior: Part 2: Social synchronisation during the development of the infant's diurnal activity-rest pattern. *Biological rhythm research*, 32(5), 529-546.
- Wulff, Porcheret, Cussans, & Foster. (2009). Sleep and circadian rhythm disturbances: Multiple genes and multiple phenotypes. *Current Opinion in Genetics & Development*.
- Zanardi, Benedetti, Di Bella, Catalano, & Smeraldi. (2000). Efficacy of paroxetine in depression is influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *Journal of clinical psychopharmacology*, 20(1), 105-107.
- Zuckerman. (1999). *Vulnerability to psychopathology: A biosocial model*: American Psychological Association.
- Zuckerman, Stevenson, & Bailey. (1987). Sleep problems in early childhood: Continuities, predictive factors, and behavioral correlates. *Pediatrics*, 80(5), 664-671.