Prenatal Exposure to Buprenorphine or Methadone: Effects on Physical Growth, Neurological Development and Temperament in Early Childhood

Volume One

Justine N Whitham BA (Hons), MPsysch (Clin)

Submitted for the award of Doctor of Philosophy in the School of Paediatrics and Reproductive Health

University of Adelaide

January 2012
# Table of Contents

Abstract .............................................................................................................................. vi
Declaration .......................................................................................................................... viii
Acknowledgements .......................................................................................................... ix
Statement of Authorship .................................................................................................... xi
List of Abbreviations and symbols .................................................................................. xiv
Glossary ............................................................................................................................. xvii

CHAPTER 1 ......................................................................................................................... 1

Literature Review ............................................................................................................... 1

1.1 A brief history of opioid use and misuse ...................................................................... 1
1.2 Opioid actions .............................................................................................................. 4
1.3 Substance dependence .............................................................................................. 5
1.4 Opioid dependence in Australia ................................................................................ 6
1.5 Associated harms of substance use and dependence ................................................... 8
1.6 Treatment of opioid dependence ................................................................................ 10
1.6.1 Methadone Maintenance Treatment .................................................................... 12
1.6.2 Buprenorphine Maintenance Treatment ................................................................ 13
1.7 Illicit opioid use in pregnancy ................................................................................... 14
1.8 Treatment of opioid dependence in pregnancy ......................................................... 17
1.8.1 Methadone ........................................................................................................... 17
1.8.2 Buprenorphine .................................................................................................... 19
1.9.1 Physical development after prenatal exposure to methadone and/or heroin .......... 25
1.9.2 Physical development after prenatal exposure to buprenorphine ......................... 32
1.10 Neurodevelopment after prenatal exposure to opioids ........................................... 34
1.10.1 Visual Evoked Potentials after prenatal exposure to methadone ....................... 35
1.10.2 Cognitive Development after prenatal exposure to methadone and/or heroin ...... 37
4.1.1 Relationship between four month growth measurements and potential confounding variables .............................................................................................................. 126
4.1.2 Four month growth measurements adjusting for potential confounding variables 127
4.1.3 Summary of infant growth at four months of age ........................................... 128
4.2 Growth of infants at 12 months of age ..................................................................... 129
4.2.1 Relationship between 12-month growth measures and potential confounding variables ............................................................................................................. 130
4.2.2 Twelve month growth measurements adjusting for potential confounding variables ................................................................................................................. 131
4.2.3 Summary of infant growth at 12 months of age ............................................. 132
4.3 Growth of infants at 24 months of age ................................................................. 133
4.3.1 Relationship between 24-month growth measures and potential confounding variables ............................................................................................................. 134
4.3.2 Twenty four month growth measurements adjusting for potential confounding variables .............................................................................................................. 135
4.3.3 Summary of infant growth at 24 months of age ............................................. 136
4.4 Longitudinal analyses of growth measurements ..................................................... 137
4.4.1 Summary of growth longitudinal analyses ..................................................... 138
4.5 Discussion ............................................................................................................... 139
CHAPTER 5 .................................................................................................................. 149
Infant Visual Evoked Potentials .................................................................................... 149
5.1 Latency of Visual Evoked Potentials at four months of age ................................. 150
5.2 Four month VEP latencies adjusting for potential confounding variables ............. 154
5.3 Summary of VEP latencies at four months of age ............................................. 156
5.4 Discussion ............................................................................................................... 156
CHAPTER 6 .................................................................................................................. 162
Bayley Scales of Infant Development ....................................................................... 162
6.1 Bayley Scales of Infant Development at 12 months of age ................................. 163
6.1.1 Relationship between 12-month Bayley Scale scores and potential confounding variables ............................................................................................................. 165
6.1.2 Twelve month Bayley Scale scores adjusting for potential confounding variables .. 166
6.1.3 Summary of Bayley Scale scores at 12 months of age ........................................... 168

6.2 Bayley Scales of Infant Development at 24 months of age ........................................ 169

6.2.1 Relationship between 24-month Bayley Scale scores and potential confounding variables .......................................................................................................................... 171

6.2.2 Twenty four month Bayley Scale scores adjusting for potential confounding variables ................................................................................................................................. 172

6.2.3 Summary of Bayley Scale scores at 24 months of age ............................................. 175

6.3 Longitudinal analyses of Bayley Scale Index Scores ....................................................... 176

6.3.1 Summary of Bayley Scale longitudinal analyses ....................................................... 178

6.4 Discussion ...................................................................................................................... 178

CHAPTER 7 ......................................................................................................................... 196

Infant Temperament ........................................................................................................... 196

7.1 Infant Temperament at four months of age ................................................................. 197

7.1.1 Relationship between four month Easy/Difficult Scale scores and potential confounding variables .................................................................................................................. 198

7.1.2 Four month Easy/Difficult Scale scores adjusting for potential confounding variables ................................................................................................................................. 198

7.1.3 Summary of Infant Temperament at four months of age ........................................ 199

7.2 Infant Temperament at 12 months of age ................................................................... 199

7.2.1 Relationship between 12-month Easy/Difficult Scale Scores and potential confounding variables ................................................................................................................ 200

7.2.2 Twelve month Easy/Difficult Scale scores adjusting for potential confounding variables ............................................................................................................................. 201

7.2.3 Summary of Infant Temperament at 12 months of age ......................................... 201

7.3 Temperament at 24 months of age .............................................................................. 202

7.3.1 Relationship between 24-month Easy/Difficult Scale scores and potential confounding variables ................................................................................................................ 202

7.3.2 Twenty Four month Easy/Difficult Scale scores adjusting for potential confounding variables .......................................................................................................................... 203

7.3.3 Summary of Infant Temperament at 24 months of age ......................................... 204

7.4 Longitudinal analyses of Easy/Difficult Scale Scores .................................................. 204

7.4.1 Summary of temperament longitudinal analyses .................................................... 205
Abstract

Pharmaceutical maintenance with methadone is the current gold standard for pregnant women with opioid-dependence. While there are many benefits of methadone, its use during pregnancy is associated with high rates of neonatal abstinence syndrome, and long term developmental and behavioural deficits in exposed infants and children. Buprenorphine is increasingly being prescribed as pharmaceutical treatment for opioid dependence due to its milder withdrawal effects, longer duration of action, and improved safety profile, compared with methadone. Although there is a growing body of research supporting the safety and efficacy of buprenorphine during pregnancy and the early neonatal period, studies of the longer term development of children exposed to buprenorphine are scarce.

This is the first study to provide comprehensive, longitudinal information about the physical growth, neurological and psychological development of Australian children prenatally exposed to buprenorphine or methadone. Participants were 30 women maintained on buprenorphine, 24 women maintained on methadone, and 33 women who were not opioid-dependent, and their children. Women were enrolled during pregnancy as part of an open-label non-randomised flexible-dosing longitudinal study, and children were assessed at four, 12 and 24 months post partum. Physical development was monitored in terms of weight, length and head circumference (HC) at each follow-up assessment. Neurological development was assessed by measuring latency of Visual Evoked Potentials (VEP) at four months of age and the Bayley Scales of Infant Development (2nd ed.) at 12 and 24 months. Care-giver ratings of child temperament were used as a measure of psychological development, and were collected at each follow-up assessment. Assessment of social, environmental and family risk factors was also undertaken.
Results showed that children prenatally exposed to buprenorphine did not differ from a non-exposed control group in their physical growth, neurological development, or temperament over the first two years of life. However, results indicated that prenatal exposure to methadone may have a pervasive influence on weight in early childhood, with children prenatally exposed to methadone continuing to have significantly lower weight, compared with non-exposed children, until two years of age. Additionally, it appears that prenatal exposure to methadone may result in significant delays to visual maturation in infancy. At four months of age, VEP latencies of infants prenatally exposed to methadone were found to be prolonged compared with those of both infants prenatally exposed to buprenorphine, and those of non-exposed infants. Scores on the Bayley Scales at 12 and 24 months of age, and caregiver-rated infant temperament at 4-, 12- and 24-months, did not differ between children prenatally exposed to methadone, buprenorphine, or non-exposed controls. Finally, regardless of substance-exposure, the quality of a child’s care-giving environment was shown to have a strong influence over infant cognitive, motor and behavioural development, while maternal-infant attachment was found to be an important predictor of child temperament.

Overall, the findings of this study suggest that maternal use of buprenorphine in pregnancy appears to be as safe as methadone in terms of early child developmental outcomes. The benefits of buprenorphine, in terms of early neurodevelopment and healthy weight gain, suggest that it should be considered as a first line treatment for opioid dependence in pregnant women. Moreover, results from this study highlight the importance of a child’s care-giving environment, and of early maternal mental health, over and above prenatal substance exposure, in shaping future developmental outcomes.
Declaration

I, Justine Nikola Whitham, certify that this work contains no material which has been accepted for the award of any other degree of diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

The author acknowledges that copyright of published works contained within this thesis (as listed below*) resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University’s digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.


Signed: ______________________________

Dated: January, 2012
Acknowledgements

Many thanks to my supervisors, Professor Michael Sawyer, Associate Professor Nicola Spurrier, Associate Professor Peter Baghurst, and Professor John Taplin. Michael, I have appreciated your guidance and expertise. Nicola, I am very grateful for having had the opportunity to work on such a wonderful project, for your support, and for your enthusiasm for this research. Peter, thank you for your judicious comments, and your willingness to answer my questions (often at short notice). John, many thanks for your encouragement and support.

Thanks to Associate Professor Fiona Arney and Associate Professor Vivienne Moore, both of whom contributed to the development of this project. Particular thanks to Fiona who was instrumental in gathering the measures and organising the initial ethics application.

Thank you to Dr Andrea Gordon for advice about the pregnancy and neonatal phase of the study, and for letting me use some of your data. Thanks also for teaching me how to spin blood samples! Thanks to Professor Jason White and Dr Olga Lopatko for advice on the pharmacological aspects of the research. Many thanks to the antenatal clinic staff at the Women’s and Children’s Hospital and Flinders Medical Centre for assistance recruiting participants, particularly Dr Anna Woods, Ann Fisk and Jo Kneebone from Drug and Alcohol Services SA, for your interest and support during recruitment.

Many thanks are due to Charlotte Goess and Cath Danz for undertaking collection of the pregnancy and neonatal data; Dr Lisa Smithers and Paul Weston for administering the visual evoked potential assessments; Kathy Moar for supervising me in the administration of the Bayley Scales; Sarah Knight and Yen Kok, for organising the interstate assessments. Thanks are also due
to Rachael Clark, Alyssa Sawyer & Femke Giessen for data entry; and Kate Dowling and Professor Phil Ryan, who provided statistical advice and support.

Thank you to the University of Adelaide and to the South Australian Department of Health for jointly funding my scholarship. This research would not have been possible without a grant from Reckitt Benckiser, who also provided funding for conference attendance.

Thanks to the staff and students of the Research and Evaluation Unit and Public Health Research Unit (past and present) for your support and encouragement; particularly thanks to my fellow PhD students, for your friendship and moral support.

Warm thanks go to the families who welcomed me into their homes, completed lengthy questionnaires, and allowed me a glimpse into their lives. Thank you for your time, your interest in the study, and your enthusiasm. This research would not have been possible without you.

Finally, I would like to thank my family and friends who have been an endless source of encouragement. Particular thanks to Mandy and Nadine who assured me that finishing was possible. To my family Janet, Peter, Alex, and Sébastien, thank you for your interest, understanding and patience. I couldn’t have finished this without your love, support and the regular doses of sanity.
Statement of Authorship

The effects of prenatal exposure to buprenorphine or methadone on infant visual evoked potentials


doi:10.1016/j.ntt.2009.09.001

Justine N Whitham\textsuperscript{a,b,*}, Nicola J Spurrier\textsuperscript{c,d}, Michael G Sawyer \textsuperscript{a,b}, Peter A Baghurst\textsuperscript{a,c,e}, John E Taplin\textsuperscript{f}, Jason M White\textsuperscript{g}, Andrea L Gordon\textsuperscript{g}

\textsuperscript{a}Discipline of Paediatrics, School of Paediatrics and Reproductive Health, The University of Adelaide, Australia

\textsuperscript{b}Research and Evaluation Unit, Women’s and Children’s Hospital, Women’s and Children’s Health Network, South Australia

\textsuperscript{c}Discipline of Public Health, School of Population Health and Clinical Practice, The University of Adelaide, Australia

\textsuperscript{d}Department of Paediatrics and Child Health, Flinders University, Australia

\textsuperscript{e}Public Health Research Unit, Women’s and Children’s Hospital, Women’s and Children’s Health Network, South Australia

\textsuperscript{f}Office of the Deputy Vice-Chancellor & Vice-President (Academic), The University of Adelaide, Australia

\textsuperscript{g}Discipline of Pharmacology, School of Medical Sciences, The University of Adelaide
WHITHAM, Justine N. (Candidate)
Ms Whitham undertook the literature searches and summaries of previous related work, collected the data, undertook statistical analyses and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

I hereby certify that the statement of contribution is accurate.

Signed ………………………………………………………………………….Date…………………

SPURRIER, Nicola J.
Associate Professor Spurrier designed the study, wrote the protocol, supervised statistical analyses and edited drafts of the manuscript.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

Signed ………………………………………………………………………….Date…………………

SAWYER, Michael G.
Professor Sawyer was involved with the study design and preparation and editing of the manuscript.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

Signed ………………………………………………………………………….Date…………………

BAGHURST, Peter A.
Associate Professor Baghurst provided statistical advice and support and edited drafts of the manuscript.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

Signed ………………………………………………………………………….Date…………………

TAPLIN, John E.
Professor Taplin contributed to preparing and editing the manuscript.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

Signed ………………………………………………………………………….Date…………………
WHITE, Jason M.
Professor White designed the initial (pregnancy) phase of the study and contributed to preparing and editing the manuscript.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

Signed ………………………………………………………………………….Date…………………

GORDON, Andrea L.
Dr Gordon was responsible for study design during the initial (pregnancy) phase of the study, collected data during the pregnancy phase and edited drafts of the manuscript.

I hereby certify that the statement of contribution is accurate and I give permission for the inclusion of the paper in the thesis.

Signed ………………………………………………………………………….Date…………………
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analyses of variance</td>
</tr>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>BF</td>
<td>Breast Feeding</td>
</tr>
<tr>
<td>BISQ</td>
<td>Brief Infant Sleep Questionnaire</td>
</tr>
<tr>
<td>BM</td>
<td>buprenorphine-maintenance</td>
</tr>
<tr>
<td>BRS</td>
<td>Behavior Rating Scale</td>
</tr>
<tr>
<td>BSID-II</td>
<td>Bayley Scales of Infant Development- Second Edition</td>
</tr>
<tr>
<td>CA</td>
<td>corrected age</td>
</tr>
<tr>
<td>cc</td>
<td>cubic centimetres</td>
</tr>
<tr>
<td>CDI-III</td>
<td>Communicative Development Inventory: Level III</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
</tr>
<tr>
<td>CYWHS</td>
<td>Children Youth and Women’s Health Service</td>
</tr>
<tr>
<td>δ</td>
<td>delta</td>
</tr>
<tr>
<td>DASSA</td>
<td>Drug and Alcohol Services South Australia</td>
</tr>
<tr>
<td>EDS</td>
<td>Easy/Difficult (temperament) Score</td>
</tr>
<tr>
<td>EPDS</td>
<td>The Edinburgh Postnatal Depression Scale</td>
</tr>
<tr>
<td>FMC</td>
<td>Flinders Medical Centre</td>
</tr>
<tr>
<td>gm</td>
<td>gram</td>
</tr>
<tr>
<td>GA</td>
<td>Gestational Age</td>
</tr>
<tr>
<td>GHQ-28</td>
<td>General Health Questionnaire</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>HOME</td>
<td>Home Observation for Measurement of the Environment</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>IGR</td>
<td>intrauterine growth restriction</td>
</tr>
<tr>
<td>ISSI-SF</td>
<td>Interview Schedule for Social Interaction - Short Form</td>
</tr>
<tr>
<td>κ</td>
<td>kappa</td>
</tr>
<tr>
<td>LAAM</td>
<td>(\iota-\alpha)-acetylmethadol</td>
</tr>
<tr>
<td>M</td>
<td>mean</td>
</tr>
<tr>
<td>MDI</td>
<td>Mental Developmental Index</td>
</tr>
<tr>
<td>MGP</td>
<td>Midwifery Group Practice</td>
</tr>
<tr>
<td>MM</td>
<td>methadone-maintenance</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>(\eta^2)</td>
<td>eta squared</td>
</tr>
<tr>
<td>NAS</td>
<td>Neonatal Abstinence Syndrome</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NDSHS</td>
<td>National Drug Strategy Household Survey</td>
</tr>
<tr>
<td>NBAS</td>
<td>Brazelton Neonatal Behavioral Assessment Scale</td>
</tr>
<tr>
<td>NYLS</td>
<td>New York Longitudinal Study</td>
</tr>
<tr>
<td>PDI</td>
<td>Psychomotor Developmental Index</td>
</tr>
<tr>
<td>PND</td>
<td>postnatal depression</td>
</tr>
<tr>
<td>PSI</td>
<td>The Parenting Stress Index</td>
</tr>
<tr>
<td>RA</td>
<td>Research Assistant</td>
</tr>
<tr>
<td>RAKIT</td>
<td>Revision of the Amsterdam Children’s Intelligence Test</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviations</td>
</tr>
<tr>
<td>SGA</td>
<td>small for gestational age</td>
</tr>
<tr>
<td>SON</td>
<td>Snijders-Oomen Nonverbal intelligence test</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>STSI</td>
<td>Short Temperament Scale for Infants</td>
</tr>
<tr>
<td>STST</td>
<td>Short Temperament Scale for Toddlers</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Association</td>
</tr>
<tr>
<td>VEP</td>
<td>Visual Evoked Potential</td>
</tr>
<tr>
<td>WCH</td>
<td>Women’s and Children’s Hospital</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WPPSI-R</td>
<td>Wechsler Preschool and Primary Scales of Intelligence – Revised</td>
</tr>
<tr>
<td>WISC-R</td>
<td>Wechsler Intelligence Scale for Children - Revised</td>
</tr>
<tr>
<td>μ</td>
<td>mu</td>
</tr>
<tr>
<td>ζ</td>
<td>zeta</td>
</tr>
<tr>
<td>Glossary</td>
<td>Definition</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Apgar score</td>
<td>A standardised measure of a baby’s condition at birth</td>
</tr>
<tr>
<td>Gravida</td>
<td>The total number of previous pregnancies</td>
</tr>
<tr>
<td>Primigravida</td>
<td>A woman pregnant for the first time.</td>
</tr>
<tr>
<td>Multigravida</td>
<td>A woman who has been pregnant more than once.</td>
</tr>
<tr>
<td>Parity</td>
<td>The total number of previous pregnancies resulting in live births or stillbirths.</td>
</tr>
<tr>
<td>Primipara</td>
<td>Pregnant woman who has had no previous pregnancy resulting in a live birth or stillbirth.</td>
</tr>
</tbody>
</table>

48’ arc or 48 min arc = 48 minutes of the retinal arc. A minute of retinal arc is a unit of angular distance with one minute of arc equal to one sixtieth of a degree.
Prenatal Exposure to Buprenorphine or Methadone: Effects on Physical Growth, Neurological Development and Temperament in Early Childhood

Volume Two

Justine N Whitham BA (Hons), MPsych (Clin)

Submitted for the award of Doctor of Philosophy in the School of Paediatrics and Reproductive Health

University of Adelaide

January 2012
# Table of Contents

List of Tables...........................................................................................................................................ii

List of Figures ...........................................................................................................................................v

Appendices..............................................................................................................................................56

Appendix A. Screening Questionnaire ................................................................................................. 56

Appendix B. Information Sheet for Maintenance Group Participants ................................................. 57

Appendix C. Consent Form for Maintenance Group Participants ......................................................... 64

Appendix D. Consent Form for Infant Participation ............................................................................... 65

Appendix E. Information Sheet for Control Group Participants .......................................................... 66

Appendix F. Consent Form for Control Group Participants ................................................................. 72

Appendix G. Initial Study Assessment .................................................................................................... 73

Appendix H. Modified Finnegan Scale ................................................................................................... 78

Appendix I. Treatment and weaning protocol for Neonatal Abstinence Syndrome ......................... 80

Appendix J. Caregiver Questionnaire .................................................................................................... 81

Appendix K. Uncontactable Letter ......................................................................................................... 116

Appendix L. Example Report .................................................................................................................. 117

Appendix M. Simple linear regressions for infant birth growth measurements, adjusting for gestational age.................................................................................................................. 119

Appendix N. Publications arising from this work ................................................................................ 121

Appendix O. Note regarding content of Chapter 5 ............................................................................. 122

References...............................................................................................................................................123
List of Tables

Table 2.1 Number of participants and retention rates for each assessment in the early childhood phase of the study ................................................................. 2
Table 2.2 Summary of data collected and measures used during each stage of the study .......... 3
Table 2.3 Sample size estimates for primary outcome variables ........................................ 5
Table 3.1 Maternal characteristics at enrolment .................................................................. 7
Table 3.2 Differences in maternal characteristics at enrolment between study participants and non participants ................................................................. 8
Table 3.3 Maternal heroin use and maintenance therapy history ........................................ 9
Table 3.4 Self reported maternal substance use during pregnancy ...................................... 10
Table 3.5 Neonatal characteristics and NAS treatment ...................................................... 11
Table 3.6 Demographic characteristics of participating infants and families ...................... 13
Table 3.7 Maternal Postnatal Attachment Scale scores, by group .................................... 15
Table 3.8 Edinburgh Postnatal Depression Scale and General Health Questionnaire scores, by group ................................................................. 16
Table 3.9 Interview Schedule for Social Interaction-Short Form scores, by group .............. 17
Table 3.10 Self-reported maternal substance use in the month prior to the four month follow-up assessment ................................................................. 18
Table 3.11 Parenting Stress Index and HOME Inventory Total Scores, by group ............... 19
Table 4.1 Anthropometry of infants at 4, 12 and 24 months of age .................................. 20
Table 4.2 Multiple Regression Analysis for variables predicting weight at four months of age ..... 21
Table 4.3 Multiple Regression Analysis for variables predicting length at four months of age ..... 22
Table 4.4 Multiple Regression Analysis for variables predicting head circumference at four months of age ................................................................. 23
Table 4.5 Multiple Regression Analysis for variables predicting weight at 12 months of age .... 24
Table 4.6 Multiple Regression Analysis for variables predicting length at 12 months of age ........ 25
Table 4.7 Multiple Regression Analysis for variables predicting head circumference at 12 months of age........................................................................................................................................................................... 26
Table 4.8 Multiple Regression Analysis for variables predicting weight at 24 months of age ........ 27
Table 4.9 Multiple Regression Analysis for variables predicting length at 24 months of age ....... 28
Table 4.10 Multiple Regression Analysis for variables predicting head circumference at 24 months of age........................................................................................................................................................................................................................................... 29
Table 5.1 Characteristics of participating women and infants, for VEP analyses ...................... 31
Table 5.2 VEP Latencies at four months of age, by group ................................................................. 33
Table 5.3 Maternal substance use, by group, for VEP analyses......................................................... 34
Table 5.4 Multiple Regression Analysis for variables predicting VEP response to 48’ checks ....... 39
Table 5.5 Multiple Regression Analysis for variables predicting VEP response to 69’ checks ....... 40
Table 6.1 Index scores of the Bayley Scales of Infant Development at 12 and 24 months of age, by group........................................................................................................................................................................................................................................... 41
Table 6.2 Multiple Regression Analysis for variables predicting MDI scores at 12 months of age . 43
Table 6.3 Multiple Regression Analysis for variables predicting PDI scores at 12 months of age... 43
Table 6.4 Multiple Regression Analysis for variables predicting BRS scores at 12 months of age .. 44
Table 6.5 Multiple Regression Analysis for variables predicting MDI scores at 24 months of age .. 45
Table 6.6 Multiple Regression Analysis for variables predicting PDI scores at 24 months of age... 46
Table 6.7 Multiple Regression Analysis for variables predicting BRS scores at 24 months of age .. 47
Table 7.1 Factor scores and Easy/Difficult Scale scores of the Short Temperament Scale for Infants, at 4 months of age, by group ........................................................................................................................................................................................................................................... 49
Table 7.2 Multiple Regression Analysis for variables predicting Easy/Difficult Scale scores at four months of age ........................................................................................................................................................................................................................................... 50
Table 7.3 Factor scores and Easy/Difficult Scale scores of the Short Temperament Scale for Toddlers, at 12 months of age, by group ........................................................................................................................................................................................................................................... 51
Table 7.4 Multiple Regression Analysis for variables predicting Easy/Difficult Scale scores at 12 months of age ................................................................. 52

Table 7.5 Factor scores and Easy/Difficult Scale scores of the Short Temperament Scale for Toddlers, at 24 months of age, by group ................................................................. 53

Table 7.6 Multiple Regression Analysis for variables predicting Easy/Difficult Scale scores at 24 months of age ................................................................. 54
List of Figures

Figure 2.1 Study design, number of participants and response rate at each stage of the longitudinal study .............................................. 1

Figure 2.2 An infant and her mother photographed after a pattern-reversal VEP test. ...................... 4

Figure 4.1 Mean weight for each group at the 4-, 12- and 24-month follow-up assessments. ...... 29

Figure 4.2 Mean length for each group at the 4-, 12- and 24-month follow-up assessments. ....... 30

Figure 4.3 Mean head circumference for each group at the 4-, 12- and 24-month follow-up assessments. ....................................................................................................................... 30

Figure 6.1 Mean MDI scores for each group at the 12- and 24-month follow-up assessment. ...... 47

Figure 6.2 Mean PDI scores for each group at the 12- and 24-month follow-up assessment. ....... 48

Figure 6.3 Mean BRS scores for each group at 12- and 24-month follow-up assessment. ............ 48

Figure 7.1 Mean EDS raw scores for each group at the 4-, 12- and 24-month follow-up assessments. ....................................................................................................................... 55

Figure 7.2 Mean EDS z-scores for each group at the 4-, 12- and 24-month follow-up assessments. ....................................................................................................................... 55