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

Volume One

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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.

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List of Abbreviations and symbols

ACh	acetylcholine
AIDS	acquired immune deficiency syndrome
ANOVA	analyses of variance
AIHW	Australian Institute of Health and Welfare
BF	Breast Feeding
BISQ	Brief Infant Sleep Questionnaire
BM	buprenorphine-maintenance
BRS	Behavior Rating Scale
BSID-II	Bayley Scales of Infant Development- Second Edition
CA	corrected age
cc	cubic centimetres
CDI-III	Communicative Development Inventory: Level III
CI	confidence interval
CNS	central nervous system
cm	centimetre
CYWHS	Children Youth and Women's Health Service
δ	delta
DASSA	Drug and Alcohol Services South Australia
EDS	Easy/Difficult (temperament) Score
EPDS	The Edinburgh Postnatal Depression Scale
FMC	Flinders Medical Centre
gm	gram
GA	Gestational Age
GHQ-28	General Health Questionnaire

HOME	Home Observation for Measurement of the Environment
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IGR	intrauterine growth restriction
ISSI-SF	Interview Schedule for Social Interaction - Short Form
κ	kappa
LAAM	ι-α-acetylmethadol
M	mean
MDI	Mental Developmental Index
MGP	Midwifery Group Practice
MM	methadone-maintenance
MRI	magnetic resonance imaging
η^2	eta squared
NAS	Neonatal Abstinence Syndrome
NHMRC	National Health and Medical Research Council
NDSHS	National Drug Strategy Household Survey
NBAS	Brazelton Neonatal Behavioral Assessment Scale
NYLS	New York Longitudinal Study
PDI	Psychomotor Developmental Index
PND	postnatal depression
PSI	The Parenting Stress Index
RA	Research Assistant
RAKIT	Revision of the Amsterdam Children's Intelligence Test
SD	standard deviations
SGA	small for gestational age
SON	Snijders-Oomen Nonverbal intelligence test

STSI	Short Temperament Scale for Infants
STST	Short Temperament Scale for Toddlers
TGA	Therapeutic Goods Association
VEP	Visual Evoked Potential
WCH	Women's and Children's Hospital
WHO	World Health Organisation
WPPSI-R	Wechsler Preschool and Primary Scales of Intelligence – Revised
WISC-R	Wechsler Intelligence Scale for Children - Revised
μ	mu
ζ	zeta

Glossary

Apgar score   A standardised measure of a baby's condition at birth

Gravida   The total number of previous pregnancies

Primigravida   A woman pregnant for the first time.

Multigravida   A woman who has been pregnant more than once.

Parity   The total number of previous pregnancies resulting in live births or stillbirths.

Primipara   Pregnant woman who has had no previous pregnancy resulting in a live birth or

stillbirth.

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.

CHAPTER 1

Literature Review

1.1 A brief history of opioid use and misuse

The term 'opioid' is used to describe both natural opiates (such as codeine and morphine) and their synthetic derivatives (including heroin and methadone). The word 'opium' originates from the Greek *opos* (juice) and *opion* (poppy juice), in reference to the Opium Poppy *Papaver somniferum* (Borg & Kreek, 1998; Hodgson, 1999). It is thought that the Egyptians used Opium Poppy extracts for pain relief and for treating diarrhoea (Simon, 2005), however, the medicinal qualities of this plant were first documented by the physician Dioscoride (circa 40-90 AD) in his pharmacopoeia *De Materia Medica*, in which he detailed its usefulness in treating pain and chronic cough, as well as the soporific properties that opium is known to possess (Hodgson, 1999).

Opium was introduced to the West from China in the mid-nineteenth century and its use became synonymous with decadence and opulence, particularly in Europe where it was romanticised by artists, writers and poets. However, in North America, use of opium was generally associated with sailors, prostitutes and other such 'degenerates' (Hodgson, 1999). It was common for people to eat or smoke raw opium until the development of patent medicines when unregulated 'concoctions', such as Laudanum (a potent mixture of alcohol and opium), became widely available (Gold & Johnson, 1998).

The principle active ingredient in opium is the alkaloid morphine, which was first isolated by Friedrich Wilhelm Sertürner in 1805 (Hodgson, 1999). However it was the synthesis of diacetylmorphine in 1874, by Charles Alder Wright at St Mary's Hospital Medical School in London, which led to the development of one of the most notorious drugs known to humankind

(Sneader, 1998). Marketed by German pharmaceutical company F Bayer & Co. in 1898 as Heroin, the drug took its name from the German *heros*, in reference to an ancient Greek demigod honoured for his heroic feats (Sneader, 1998). This new 'wonder-drug' was originally utilised as a cough suppressant and respiration aid for patients with tuberculosis, and, ironically, a possible cure for morphine addiction (Gold & Johnson, 1998; Hodgson, 1999; Sneader, 1998). Along with cough suppression, opioids exert their effects on pain and mood through the central nervous system (CNS). Opioids are powerful analgesics and have the ability to decrease anxiety, elevate mood and increase drowsiness (Simon, 2005). Because of these effects, heroin was often the key ingredient in popular 'health tonics' and 'cordials' which were recommended for many conditions including earache, haemorrhoids, morning sickness, cholera, and were also marketed as soothing syrups for unsettled infants (Hodgson, 1999).

When first introduced to the medicinal market, heroin was usually prescribed in oral doses too small to cause habituation or, in the cases of chronic lung disease; patients were continually medicated, thus keeping withdrawal symptoms at bay. However, as its sale was unregulated, social use of heroin escalated and warnings about the addictive properties of heroin began to appear (Sneader, 1998).

With the development of the hypodermic needle in the mid nineteenth century, intra-venous delivery of opioids became possible. When opioids are administered directly into the circulation there is a rapid increase in opioid levels in the brain which can induce an intense, euphoric sense of well-being, known as a 'rush' or 'high' (Gold & Johnson, 1998; Hodgson, 1999; Jaffe, Knapp, & Ciraulo, 1997).The desire to experience this extreme state of pleasure is thought to be the motivation behind the repeated self-administration of heroin, as well as the irrationality that often accompanies the drug-seeking behaviour of addicted individuals (Gold & Johnson, 1998; Jaffe, et al., 1997).

From the late 1800s to the early 1900s, it was common in the United States for physicians to prescribe medications and 'tonics' containing opiates to women suffering from 'female complaints', including gynaecological problems and 'nervous weakness'. Additionally, patent medicines and 'home remedies' (many containing heroin) were widely promoted through women's magazines, and were available without prescription via mail-order catalogues. This widespread availability and over-prescription of opiates often led to addiction, with early US surveys suggesting that between 50-75% of chronic opiates users were women, often of white, middle- to upper-class background. Society usually turned a blind eye to the 'drug habits' of these women as long as they were 'acceptable' members of the community (Kandall, 1996). At the beginning of the twentieth century, various drug laws and legislations restricted the trafficking of substances, and society began to view opiate use as objectionable. Along with tighter controls of opioids in Europe and North America, this meant that by the 1920s opium and morphine were no longer available without prescription (Hodgson, 1999).

In order to provide treatment for individuals addicted to opioids and reduce crime associated with the illicit trade of narcotics, public outpatient clinics were set up in the United States to dispense morphine and heroin at low cost to clinic registrants. The largest facility, in New York City, treated just over 1, 500 women (23% of its patients) in its seven months of operation in 1919, many of whom were white and under the age of 40. Records of similar clinics around the country indicate that between 25 and 57% of patients were female (Kandall, 1996).

In contrast to the latter half of the 19th century, by the 1940s the majority of America's opioid users were men, and the typical 'profile' of female opioid users was changing. Women who sought treatment for opioid addiction between 1920 and 1940 in the United States were likely to be white, Protestant, rural housewives in their early 40s. Most had acquired their long-standing addiction (usually to morphine) through prescribed treatment for a psychosomatic or physical illness. Over the next forty years opioids were increasingly used for recreational purposes, with up

to two thirds of female opioid-users citing 'curiosity' or peer influences as the reasons for trying

drugs. Women began to seek treatment for opioid addiction earlier and heroin was more

frequently the drug of choice. By the 1970s and 1980s, women comprised 20-30% of opioid users

in the United States (Kandall, 1996). This figure has remained relatively stable in recent years and

is similar to rates of opioid use by women cited in Australian and international studies (Anderson,

2006; Australian Institute of Health and Welfare, 2011)]. While there does not appear to be

comprehensive information available about the history of women and opioid addiction in

Australia, it is possible that use of opioids by Australian women has mirrored that of their

American counterparts.

1.2 Opioid actions

Opioids produce their pharmacological effects by binding to opioid receptors located on the

membranes of neurons and other cells in the body. The three principle classes of opioid receptors

are mu (μ), delta (δ), and kappa (κ), with various subtypes within each class. Because these opioid

receptors are found throughout the brain and spinal cord, as well as other organ sites, opioids

exert their effects on many of the organ systems in the body (Farid, Dunlop, Tait, & Hulse, 2008;

Jaffe, et al., 1997). When activated, μ-opioid and δ-opioid receptors appear to influence analgesia,

sedation, blood pressure, reinforcing effects, along with endocrine and gastrointestinal function;

while activation of κ –opioid receptors can produce analgesia and endocrine changes (Jaffe, et al.,

1997).

Opioid drugs are categorised in terms of their capacity to bind with and activate different classes

of receptors. It is thought that drugs produce their effects by mimicking the post-synaptic

stimulation of the endogenous opiate peptides that are neurotransmitters in the brain (Kolb &

Wishaw, 1996). Drugs that produce a biological effect after binding to and activating a receptor

are known as *agonists*, those that bind to a receptor but produce less than full receptor activation

are known as *partial agonists*, while *antagonists* bind to a receptor but do not activate it and may also block the effects of agonists (Jaffe, et al., 1997; Zacny & Walker, 1998).

While medically managed oral doses of opioid drugs are unlikely to result in major toxic effects, the protracted use of illicit, and often contaminated opioids, particularly those administered intravenously, can be associated with severe and sometimes fatal consequences (Jaffe, et al., 1997).

1.3 Substance dependence

Substance dependence is characterised by a combination of physiological, cognitive and behavioural symptoms, with an individual persisting in the use of substances despite significant problems associated with their use. In a dependent individual, consequences of repeated self-administration can be tolerance to the substance, withdrawal symptoms with the cessation of use, and compulsive drug-taking behaviours (American Psychiatric Association, 2000; Simon, 2005).

Tolerance refers to the requirement for increasing quantities of a substance in order to achieve a desired effect, or to a marked reduction in the effect of a substance with continued use of the same dosage. Withdrawal refers to maladaptive behavioural changes, characterised by concurrent physical and psychological symptoms that occur with the cessation of, or reduction in, substance use after a sustained period of heavy use. Physical symptoms of opioid withdrawal include fever, nausea, muscle and bone pain, diarrhoea, pupillary dilation, piloerection, and yawning; while psychological withdrawal symptoms can include drug cravings, dysphoric mood, anxiety, and irritability. In order to relieve or completely avoid these symptoms an individual needs to take the same, or a closely related, substance (American Psychiatric Association, 2000; Jaffe, et al., 1997).

Whilst a diagnosis of substance dependence does not require the presence of tolerance or withdrawal, previous occurrence of either is suggestive of a clinical pattern of dependence (i.e., early onset, high substance intake, and large number of substance-related problems). Compulsive substance use that is characteristic of dependence includes any number of features. Individuals may take larger amounts of a substance, or take a substance over a longer period, than they initially intended. There may be a persistent desire to control, reduce, or discontinue substance use, often with many unsuccessful attempts. Individuals may spend substantial amounts of time engaged in activities to obtain and use the substance, or recovering from its effects. In severe cases of substance dependence, the majority of a person's daily activities may be centred on the need to procure and use the substance. Individuals may reduce or withdraw from social, occupational and recreational activities in order to be able to use the substance. Finally, use of the substance may continue despite awareness that physical or psychological problems are likely to have been caused or exacerbated by continuing substance use (American Psychiatric Association, 2000).

1.4 Opioid dependence in Australia

Research indicates that, globally 185 million adults (4.5% of the global population aged 15-64 years) are current consumers of illicit drugs, with 15.3 million (0.4% of the global adult population) using illicit opioids, and 15.2 million injecting drug users (Anderson, 2006). While it is difficult to estimate the worldwide numbers of women who use illicit opioids, it has been suggested that of the 15.3 million adults with substance use disorders, almost 25% (3.6 million) are women (Anderson, 2006). In a study of prevalence estimates of lifetime substance use across seven international sites, Vega et al. (2002) reported that between 0.1 -4.4% of women reported illicit opioid use. Recent epidemiological surveys suggest that between 0.3-0.7% of the Australian community use illicit opioids, of whom, approximately one third are women (Australian Institute of Health and Welfare, 2008, 2011; Hall, Ross, Lynskey, Law, & Degenhardt, 2000; McBride et al., 2009; Teesson, Baillie, Lynskey, Manor, & Degenhardt, 2006). McBride et al. (2009) have shown

that the prevalence of drug use and dependence, and the conditional prevalence of dependence

(i.e. prevalence of dependence amongst past year users only) in adults aged 18-54, was

significantly higher in Australia than in the United States of America (USA). Using data from two

cross-sectional nationally representative household surveys (the Australian National Survey of

Mental Health and Well-Being, 1997 and the American National Epidemiologic Survey on Alcohol

and Related Conditions, 2001-2002) they found that 10.8% of Australians and 5.2% of Americans

reported using at least one illicit drug (including cannabis, stimulants, sedatives and opioids) in

the previous 12 months. The rate of self-reported opioid use was higher amongst American

respondents than for the Australian population, with 1.2% and 0.3% of respondents from the

respective surveys indicating that they had used opioids in the previous 12 months. The

percentage of respondents who met Diagnostic and Statistical Manual of Mental Disorders, 4th

Edition (DMS-IV) criteria for dependence on any drug within the previous 12 months was 2.7% in

the Australian sample and 0.7% in the American sample, with the estimated past year prevalence

of opioid dependence 0.3% for the Australian sample and 0.2% for their American counterparts.

The prevalence of conditional dependence on opioids differed substantially between the two

samples, with Australian opioid users over six times more likely to meet dependence criteria than

American opioid users. The authors suggested that differing societal and political attitudes

towards drugs may influence patterns of substance use in each country. However, the Australian

data was collected more than 10 years earlier than the data in the American study and it is

possible that patterns of substance use in Australia have changed over this time (McBride, et al.,

2009).

Data from the 2007 AIHW National Drug Strategy Household Survey (NDSHS) (Australian Institute

of Health and Welfare, 2008) indicated that trends in illicit-opioid use remain similar to that

reported in the 1997 Australian National Survey of Mental Health and Well-Being. The 2007

NDSHS found that almost 350,000 Australians aged 14 years or older (2%) reported using opioids

(heroin, methadone and/or buprenorphine for non-maintenance purposes, other opioids for non-

medical purposes) during their lifetime. Almost twice as many males as females reported use of illicit opioids within the 12 months prior to the survey (36,800 versus 20,200; 0.3% of the population). While separate data was not provided for the proportion of males and females who had recently used other opioids, 14,000 males and 4,900 females (0.1% of the population) reported illicit heroin or methadone use within the previous week. The highest proportion of respondents reporting illicit opioid use was aged 20-29 years, with 2.7% (79,000) of this group reporting lifetime use and 0.6% (19,100) reporting use in the previous 12 months. Sixty percent of recent users aged 14 years or older, reported using heroin, methadone and/or other opioids for non-medical purposes weekly or more frequently. Recent heroin users averaged 2.6 'hits' of heroin on days used, with the majority (90%) using heroin intravenously, and almost 70% using it in their own home. The majority of recent methadone users reported one dose of methadone on days used, with 74% reporting intravenous use. The mean reported age for first heroin use was 21.9 years, whilst for methadone it was 23.3 years of age (Australian Institute of Health and Welfare, 2008). Whilst age of initiation was not provided separately for use of other opioids, the 2010 NDSHS found that the mean age for use of any illicit pharmaceutical (including analgesics, tranquilisers, steroids along with non-prescribed use of methadone, buprenorphine and other opioids) was 23.7 years (Australian Institute of Health and Welfare, 2011).

1.5 Associated harms of substance use and dependence

In terms of problematic illicit drug use, opioids are the primary contributor to increasing burdens on public order and public health worldwide (Anderson, 2006). There is a high cost associated with the continued use of illicit substances, with recent data from the Illicit Drug Reporting System (IDRS) indicating that the median price of a gram of heroin ranged between $300 to $600, and the median price of a 'cap' (a typical amount used in a single injection or 'hit') was $50 (O'Brien et al., 2007). The IDRS also found that 45% of injecting drug users interviewed reported they had engaged in some kind of criminal activity (most commonly drug dealing or property crime) within the month prior to participating in the survey, and 43% reported having been

arrested within the previous 12 months (O'Brien, et al., 2007). In a recent AIHW report (2007),

heroin accounted for four percent of all arrests relating to illicit drugs in 2004-05 (including

dealing, trafficking, possession and use), and 62% of arrests related specifically to use or

possession of illicit drugs. In 2005, 10% of sentenced prisoners were incarcerated for a drug-

related offence, whilst amongst adults apprehended by police, approximately 18% tested positive

to illicit opioids (Australian Institute of Health and Welfare, 2007).

The most recent Burden of Disease and Injury in Australia study (Begg et al., 2007), estimated that

illicit drugs were responsible for 2.0% of the total burden of disease in Australia, an increase of

0.2% from 1996 (Begg, et al., 2007; Mathers, Vos, & Stevenson, 1999). Substance use is associated

with significant risks to physical and mental health attributable to individual substances, poor

nutrition and hygiene, and health risk behaviours. The IDRS found that 38% of injecting drug

users surveyed reported experiencing a mental health problem, other than drug dependence, in

the six months prior to interview. Twenty seven percent of the sample reported experiencing

depression, with anxiety the next most commonly reported mental health problem. Of those

reporting mental health problems, 70% had consulted a health professional within the six months

prior to participating in the survey (O'Brien, et al., 2007).

Sixty-five percent of the national sample of injecting drug users reported experiencing injecting-

related health problems in the month preceding participating in the survey (O'Brien, et al., 2007).

These problems included significant bruising, scarring, and difficulty injecting, the latter being an

indication of poor vascular health. Approximately one third of participants reported sharing

needles or other injecting equipment in the month prior to interview (O'Brien, et al., 2007).

Through equipment sharing, injecting drug users are at significant risk of blood-borne viruses,

such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV).

In 2005, 61% of people attending needle and syringe program sites tested positive to HCV, with

the prevalence of HCV increasing with longer duration of injecting drug use. This is in comparison

to the prevalence of HCV in the general population, which is estimated to be only two percent. In 2005, 16% of new acquired immune deficiency syndrome (AIDS) diagnoses were amongst people with a history of injecting drug use (Australian Institute of Health and Welfare, 2007).

Opioid use is also associated with risk of overdose. Of the injecting drug users surveyed in the IDRS who reported heroin use within the previous six months, 59% reported overdosing at least once within their lifetime (O'Brien, et al., 2007). In 2004-05 the number, per million persons, of opioid-related hospital admissions among 15 to 54 year olds was 415; with the rate of accidental opioid-related death (in which opioids were considered the primary cause of death) 32.5 per million persons aged 15 to 54 years.

Substance related harm is not directed solely at the user. In 2006, 21% of injecting drug users reported that they had become verbally aggressive after using heroin (O'Brien, et al., 2007), whilst the 2007 National Drug Strategy Household Survey found that 14.6% of Australians aged 14 years or older reported having been abused or 'placed in fear' by someone affected by illicit drugs (Australian Institute of Health and Welfare, 2008).

1.6 Treatment of opioid dependence

Opioid dependence is a serious medical condition, with physiological and psychological elements, that is often chronic in nature. Many opioid users find it difficult to control their addiction and experience multiple relapses following treatment or attempted abstinence. There are several treatment options available for those wishing to cease opioid use. Some methods, such as treatment with antagonist therapies, therapeutic communities and supported self-help groups, are 'abstinence-based' and aim for complete, often rapid, cessation of opioid use; whilst others involve medically managed detoxification or pharmaceutical maintenance programs (O'Brien, 2004; Verster & Buning, 2005). Maintenance pharmacotherapies, in combination with ongoing

psychological counselling and support, have been shown to be the most effective of these treatments for opioid dependence (Verster & Buning, 2005).

While treatment with antagonist therapies and involvement in residential programs have shown to reduce heroin use in the short term, many individuals return to illicit opioid use due to unwanted side effects or lack of support. Rates of relapse to illicit opioid use following detoxification are also high, if additional treatment or support is not continued (Gold & Johnson, 1998; O'Brien, 2004; Verster & Buning, 2005). For example, in an American study of 116 adults admitted to a short-term (3-day) inpatient detoxification program, only 13% remained abstinent from heroin use within the first month post detoxification and 25% reported a return to daily use of heroin within six months (Chutuape, Jasinski, Fingerhood, & Stitzer, 2001). Additionally, of 66 participants who were assessed for latency-to-relapse, 26% reported heroin use on the day they were discharged from the program. This study also found significantly lower rates of self-reported days of heroin use, incarceration rates, and positive drug screens for participants who engaged with other forms of treatment (i.e. methadone programs, drug-free treatment) during the six-month follow-up, compared with those who did not engage in other treatment (Chutuape, et al., 2001).

While the long term objective of pharmaceutical maintenance is to assist an individual to discontinue illicit opioid use, the short term goals of treatment focus on harm reduction and public health. The aims of maintenance medication include: 1) reduction in a person's use of illicit substances, 2) improvement in the person's health and well being, 3) minimisation of the risks associated with injecting drug use, including the spread of blood-borne viruses and the risk of overdose, 4) decreasing criminal activity associated with illicit opioid use, and 5) facilitation of social rehabilitation through removing the individual from a drug-seeking environment (Henry-Edwards et al., 2003; Verster & Buning, 2005).

In Australia, individuals with opioid-dependence have had the option of treatment with maintenance pharmacotherapies since the late 1960s. In June 2009, there were 43,445 individuals in Australia registered as participants in opioid maintenance programs, with 70% registered as receiving methadone maintenance treatment (MM), and the remainder receiving buprenorphine maintenance treatment (BM). Currently, the provision of these medications is funded by the Australian Government and they are delivered through pharmacies and clinics within a holistic treatment framework that includes medical management along with psychological and social assistance (Australian Institute of Health and Welfare, 2010).

In South Australia in June 2009, there were 3,151 people registered as receiving pharmacotherapy maintenance, 62% of whom were receiving MM and the remainder receiving BM. Sixty four percent of South Australian registrants were male, and 53% were aged 20-39 years. These are similar to the proportions in national samples (Australian Institute of Health and Welfare, 2010).

1.6.1 Methadone Maintenance Treatment

Methadone hydrochloride is a synthetic narcotic analgesic which was first synthesised in Germany in the 1930s. Patented in 1941, it was further developed after World War II and was studied as an analgesic and withdrawal treatment for heroin addiction when it was found to possess similar properties to morphine (Borg & Kreek, 1998; Lowinson et al., 2005). Methadone was initially trialled as a maintenance treatment for heroin dependence in the United States in 1964-65. When administered in adequate oral doses every 24-36 hours it stabilised individuals addicted to heroin without inducing euphoria, sedation or analgesia. It was also medically safe, tolerable, relieved drug cravings, and 'blocked' the narcotic effects of short acting opioids, such as heroin (Dole & Nyswander, 1965; Lowinson, et al., 2005). Methadone was approved for use as a maintenance medication for opioid dependence by the United States Food and Drug Administration (FDA) in 1972. It was introduced to Australia for this purpose in 1969. With adjunct treatment, such as counselling and social services, methadone maintenance has become the 'gold standard' for

treatment of illicit opioid dependence internationally (Farid, et al., 2008; Henry-Edwards, et al., 2003).

Methadone is a full agonist at μ-opioid receptors and thus produces similar effects to morphine, but with a longer duration of action (R. E. Johnson, Strain, & Amass, 2003; Lowinson, et al., 2005). Because it has good oral bioavailability and a long elimination half-life, methadone is usually administered in a single daily oral dose (Australian Drug Foundation, 2005b; Henry-Edwards, et al., 2003; R. E. Johnson, Strain, et al., 2003). Side effects of methadone maintenance, such as opioid intoxication, lethargy and pinpoint pupils, are usually observed in the early stage of treatment, but abate with dose adjustment. However, withdrawal symptoms may be experienced if a dose is missed. Due to methadone's full agonist properties there is no 'ceiling' to the level of respiratory depression or sedation that it can induce, and overdose can be fatal (Mattick, Kimber, Breen, & Davoli, 2003). Ongoing complaints for people maintained on methadone can include dry mouth, constipation, increased sweating, reduced libido, and irregular menstruation or amenorrhea in women (Henry-Edwards, et al., 2003; Lowinson, et al., 2005). Additionally, individuals with opioid-dependence may view methadone maintenance in an unfavourable light, or experience stigma associated with its use (Anstice, Strike, & Brands, 2009; Mattick, et al., 2003; Murphy & Irwin, 1992).

1.6.2 Buprenorphine Maintenance Treatment

Buprenorphine hydrochloride is a semi-synthetic derivative of the morphine alkaloid thebaine (Reisinger, 1985). It was initially developed in the 1970s and used as an analgesic for acute pain management (Verster & Buning, 2005). Research published in 1978 (Jasinski, Pevnick, & Griffith, 1978) was the first to propose that buprenorphine could be used for the treatment of opioid-dependence, and to demonstrate that it had a low physical abuse potential and mild withdrawal syndrome (Fudala & O'Brien, 2005; Lintzeris et al., 2006; Mattick, et al., 2003; Reisinger, 1985). Buprenorphine was first registered for treatment of opioid dependence in France in 1995, and

was registered in Australia by the Therapeutic Goods Association (TGA) for maintenance and detoxification purposes in 2000 (Lintzeris, et al., 2006; O'Brien, et al., 2007).

Buprenorphine is a partial agonist at μ-opioid receptors, and an antagonist at κ-opiate receptors. It has an analgesic potency up to 50 times that of morphine (Fudala & O'Brien, 2005; Lintzeris, et al., 2006; Mattick, et al., 2003; Reisinger, 1985). Because of its partial agonist properties and slow dissociation from opioid receptors, buprenorphine blocks the effects of full opioid agonists over a prolonged period of time. Its opiate-like effects are weaker than those of a pure agonist, and do not induce strong feelings of euphoria, and there is a lower risk of abuse, addiction and unwanted side effects. Unlike methadone, there is a 'ceiling effect' of buprenorphine on respiratory depression and sedation. Buprenorphine has poor bioavailability and is administered in a sublingual tablet. At high doses it has a longer duration of effect than methadone which allows for alternate-day or thrice-weekly dosing regimens. Buprenorphine's long duration of action also results in a delayed withdrawal syndrome that appears to be milder than that of heroin, morphine or methadone (Davids & Gastpar, 2004; Fudala & O'Brien, 2005; Lintzeris, et al., 2006; Reisinger, 1985).

1.7 Illicit opioid use in pregnancy

A large proportion of the drug-using population, both in Australia and overseas, are young adults, and many are women of childbearing age (Adams, Gfroerer, & Rouse, 1989; Australian Institute of Health and Welfare, 2008, 2010; Berlin et al., 1998; Chang, Carroll, Behr, & Kosten, 1992; Hoare, 2009; R. E. Johnson, Jones, & Fischer, 2003; Kayemba-Kay's & Laclyde, 2003; Laken, McComish, & Ager, 1997; Lejeune, Simmat-Durand, Gourarier, & Aubisson, 2006; McBride, et al., 2009; Teesson, et al., 2006). Accurate estimation of the proportion of women using illicit substances during pregnancy is difficult, not least because collecting this information frequently relies on voluntary disclosure (Oei & Kei, 2007). However, recent data from the United States suggested that 4.5% of pregnant women aged 15 to 44 years had used an illicit substance in the previous

month (Substance Abuse and Mental Health Services Administration, 2010). While prevalence of opioid use was not reported, an earlier survey of birth records in Oregon found that maternal substance use was evident in 5.2% of singleton deliveries and that 6% of substance-using women reportedly used heroin whilst pregnant (Slutsker, Smith, Higginson, & Fleming, 1993). Other North American studies have shown that between 1% and 2.3% of all infants are exposed to opiates prenatally (C. R. Bauer et al., 2002; Finch, Vega, & Kolody, 2001; Lester et al., 2001).

The prevalence of illicit substance use by pregnant women appears to be much lower in the United Kingdom (UK), with only 0.9% of women attending at a Welsh maternity unit reporting substance use during their pregnancy (Goel, Beasley, Rajkumar, & Banerjee, 2010). which is similar to that reported in earlier research in the UK (Northern and Yorkshire Public Health Observatory, 2002). Recent Australian research suggests that, in New South Wales and the Australian Capital Territory, 1.3% of women report use of illicit substances during pregnancy, and that 5% of infants admitted to neonatal intensive care units are prenatally exposed to illicit substances (Abdel-Latif, Bajuk, Lui, & Oei, 2007; Oei & Kei, 2007). Kennare, Heard and Chan (2005) found that substance use during pregnancy was reported by 0.8% (707/ 89,080) of women who delivered in South Australia between 1998 and 2002. An audit of 144 of these cases found that almost 40% of women reported use of marijuana whilst pregnant, 30% used methadone (including for maintenance reasons), 12.5% reported heroin use and 2.1% reported using other opioids during their pregnancy (Kennare, et al., 2005).

Prenatal exposure to illicit opioids has been shown to increase the risk of poorer outcomes for both mothers and infants, compared with non-exposed populations (Adams, et al., 1989; Chang, et al., 1992; Farid, et al., 2008; Kaltenbach, Berghella, & Finnegan, 1998). Women who use illicit opioids in pregnancy experience a high rate of obstetric complications, often because of poor attendance or non compliance with antenatal care. Complications for pregnant substance-dependent women can include poor intra-uterine growth, toxaemia, miscarriage, premature

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labour, and antepartum haemorrhage (Adams, et al., 1989; Australian Drug Foundation, 2005a; Kaltenbach, et al., 1998; Kennare, et al., 2005; Morse, Weiner, & Garrido, 1989; Sobrian et al., 1989). Fluctuations in maternal drug levels, due to the continued cycling between states of intoxication and withdrawal, place increased stress on the developing foetus (Fischer et al., 2000; Kaltenbach, et al., 1998). Prenatal exposure to illicit opioids has also been associated with increased risk of prematurity, low Apgar scores, low birth weight, being small for gestational age, neurobehavioural problems and an increased risk of sudden infant death syndrome (SIDS), compared with non-exposed infants (Berlin, et al., 1998; Chang, et al., 1992; Kandall et al., 1976; Koren, Matsui, Einarson, Knoppert, & Steiner, 2005; Laken, et al., 1997; Robins & Mills, 1993; Sobrian, et al., 1989). Infants exposed to opioids in pregnancy are also at high risk of developing infant withdrawal symptoms, or neonatal abstinence syndrome (NAS) (Finnegan, 1990; Finnegan & Kandall, 1997; Kaltenbach, 1994; Kandall et al., 1977). NAS develops when infants who are prenatally exposed to opioid agonists become passively dependent and subsequently undergo opioid withdrawal upon delivery. NAS is characterised by hyperirritability of the central nervous system. Symptoms among infants include high-pitched crying, frantic fist sucking, poor feeding, regurgitation, diarrhoea, hyperactive reflexes, tremors, sweating, nasal stuffiness, skin mottling, fever, respiratory distress, and convulsions (Finnegan, 1990; Finnegan & Kandall, 1997; Kaltenbach & Finnegan, 1986). These symptoms are generally acute and can be managed with pharmacological treatment. However, prolonged hospital stays for substance-exposed newborns are common as onset of NAS can be delayed. Current clinical guidelines therefore recommend that infants are observed by medical staff for up to 10 days post delivery to prevent unsupervised withdrawal which may be fatal (New South Wales Department of Health, 2006b).

Given these problematic outcomes, complete abstinence from opioid use during pregnancy is the 'ideal' objective. However, in the majority of cases, total abstinence is an unrealistic goal, particularly if the woman's partner is also substance-dependent. Rates of relapse to illicit opioid use after detoxification attempts are high (Dashe, Jackson, Olscher, Zane, & Wendel, 1998; Jones,

O'Grady, Malfi, & Tuten, 2008; Luty, Nikolaou, & Bearn, 2003) and illicit opioid use has been

associated with increased rates of infant morbidity and mortality (Finnegan & Kandall, 1997). In

order to assist a pregnant opioid-dependent woman to abstain from illicit drug use and the

associated lifestyle, current best practice is maintenance with a long-acting pharmaceutical

maintenance opioid (Fischer, et al., 2000; Kakko, Heilig, & Sarman, 2008; Kaltenbach, et al., 1998).

1.8 Treatment of opioid dependence in pregnancy

1.8.1 Methadone

In Australia, medical maintenance with methadone hydrochloride is the first line treatment for

pregnant women with opioid-dependence (Dunlop et al., 2003; Farid, et al., 2008; Lintzeris, et al.,

2006). Benefits for women maintained on methadone during pregnancy include increased

likelihood of attendance at antenatal care appointments, reduction in obstetric complications,

stabilisation of plasma drug concentrations across the day, improvement in maternal nutrition,

and engagement in a more balanced and stable lifestyle (Australian Drug Foundation, 2005b;

Chang, et al., 1992; Dunlop, et al., 2003; Lejeune, et al., 2006; Lifschitz, Wilson, Smith, &

Desmond, 1985; Lintzeris, et al., 2006). Infants prenatally exposed to methadone have been

shown to have better outcomes than heroin-exposed infants in terms of the proportion who are

born small for gestational age (SGA), have low birth weight, or have problems related to feeding,

settling and hypertonicity (Kandall, et al., 1976; Lifschitz, Wilson, Smith, & Desmond, 1983;

Wilson, 1989; Wilson, Desmond, & Wait, 1981; Wilson, McCreary, Kean, & Baxter, 1979).

However, whilst treatment with methadone during pregnancy results in fewer complications for

both mothers and infants when compared to use of illicit opioids, maternal methadone use has a

number of detrimental effects (R. E. Johnson, Jones, et al., 2003). Kandall et al. (1976) found that

the birth weight of infants exposed to maintenance methadone (n=106), while significantly higher

than that of infants exposed to heroin (n=153), was significantly lower than that of control infants

(n=66). This same study also reported that the gestational age of infants exposed to methadone

did not differ significantly from that of infants exposed to heroin, and furthermore, was significantly lower than that of infants in the control group (Kandall, et al., 1976).

Prenatal exposure to methadone maintenance (MM) is associated with high rates of NAS (60-90% of methadone maintained pregnancies) (Finnegan & Kandall, 1997; Lundgren, Fitzgerald, Young, Amodeo, & Schilling, 2007). Greater duration and severity of NAS have been recorded in infants undergoing withdrawal from methadone when compared with infants undergoing withdrawal from heroin alone (Jarvis & Schnoll, 1995). Lifschitz et al. (1983) reported prolonged symptoms of NAS for infants prenatally exposed to methadone (n=21, $M{\pm}SD$ =25.3±14.0 days) compared with infants prenatally exposed to heroin (n=22, $M{\pm}SD$ =13.5±12.9 days, ns). Wilson and colleagues (Wilson, 1989; Wilson, et al., 1981) described the prevalence and severity of NAS in infants exposed to methadone (n=39) as comparable to that of infants exposed to heroin (n=30). However in this study, a greater percentage of methadone-exposed infants experienced NAS symptoms (100% vs. 83%) and required a significantly longer course of treatment than infants exposed to heroin ($M{\pm}SD$ =30±14 days vs. $M{\pm}SD$ =20±16 days, t=2.76, p<.01) (Wilson, 1989; Wilson, et al., 1981).

In a study examining the early neonatal period of infants exposed to opioids, Kandall and colleagues (1977) reported that NAS symptoms were experienced with similar frequency by three groups of infants (i) prenatally exposed to heroin (n=61, 79%), (ii) prenatally exposed to methadone (n=86, 86%), and (iii) prenatally exposed to both heroin and methadone (n=59, 85%). A greater percentage of infants prenatally exposed to methadone (77%) required pharmacological treatment for NAS symptoms, compared with the heroin-exposed (43%) and the methadone/heroin-exposed (m/h) groups combined (68%, p<.001). Infants prenatally exposed to methadone required significantly higher doses of pharmacological treatment ($M{\pm}SE$ =0.31±0.01 cc) than the other two groups combined (heroin: $M{\pm}SE$ =0.21±0.01 cc; m/h: $M{\pm}SE$ =0.26±0.01 cc, p<.001) and required treatment over a greater period of time (methadone: $M{\pm}SE$ =29.2±8.8 days)

compared with the other two groups combined (heroin: $M \pm SE$ =10.8±2.6 days; m/h: $M \pm SE$

=20.8±1.6 days, $p<.001$) (Kandall, et al., 1977).

Methadone is readily transferred from the mother to the developing foetus, via the placenta, and

it is retained in placental tissue. It is thought that placental disposition of methadone may affect

the incidence and severity of NAS symptoms (Nekhayeva et al., 2005). It is unclear as to whether

maternal methadone dose at delivery is positively associated with the severity of infant NAS. Levy

and Spino (1993) reported that severity of NAS appeared unrelated to maternal methadone dose;

however Doberczak, Kandall, and Wilets (1991) reported a positive correlation between maternal

methadone dosage and the severity of NAS across a wide range of gestational ages.

1.8.2 Buprenorphine

Buprenorphine hydrochloride is now widely used in the treatment of non-pregnant opioid-

dependent individuals. A number of observational studies have supported its safety and efficacy

during pregnancy and the early neonatal period [see (R. E. Johnson, Jones, et al., 2003) for a

review]. However, these studies have been limited by low subject numbers (i.e. N= 1 to 24) and

lack comparison with existing treatments or non-exposed controls (Fischer, et al., 2000; R. E.

Johnson et al., 2001; Kayemba-Kay's & Laclyde, 2003; Lejeune, et al., 2006; Marquet, Chevrel,

Lavignasse, Merle, & Lachatre, 1997).

Results from larger, more recent studies are now available(Czerkes, 2010; Ebner et al., 2007;

Fischer et al., 2006; Jones et al., 2005; Jones et al., 2010; Kahila, Saisto, Kivitie-Kallio, Haukkamaa,

& Halmesmaki, 2007; Kakko, et al., 2008; Lejeune, et al., 2006). The following section provides an

overview of this research. First, studies using retrospective case-note review and less well

controlled prospective studies are discussed. This is followed by discussion of randomised-

controlled trials.

A recent unpublished study retrospectively reviewed the case notes of 68 women maintained on buprenorphine and 101 women maintained on methadone during pregnancy in Portland, Maine (Czerkes, 2010). Included in the study were all infants delivered beyond 37 weeks gestation at the Maine Medical Centre between 2004 and 2008. It was reported that the mean NAS score of infants prenatally exposed to buprenorphine was significantly lower than that of infants prenatally exposed to methadone (10.7 vs. 12.5, $p<.01$), and 50% of BM infants required treatment for NAS compared with 75% of MM infants ($p<.001$). This study also found that infants prenatally exposed to methadone had a significantly longer length of hospital stay than infants prenatally exposed to buprenorphine (MM=15.7 days vs. BM=8.4 days, $p<.001$) (Czerkes, 2010). No statistically significant differences between the groups in terms of in maternal characteristics (e.g. comorbidity, maternal age, mode of delivery) were found, and although it was reported that data on infant gestational age at delivery, birth weight, and Apgar scores was collected, this information was not available (Boughton, 2010; Czerkes, 2010).

In a prospective study of 66 Finnish women maintained on buprenorphine throughout their pregnancies, Kahila et al. (2007) reported that the prevalence of premature delivery, caesarean section, low Apgar scores and low umbilical artery pH was comparable to national Finnish averages. However, infants in the study had significantly lower birth weights and longer hospital stays than the national average in Finland. A high rate of NAS (76%) and a higher than expected rate of sudden infant deaths (2/67 compared with a national incidence of 0.19/1000) was also reported (Kahila, Saisto, et al., 2007). Kakko et al. (2008) prospectively followed a consecutive sample of 47 pregnancies in 39 women maintained on buprenorphine in Stockholm between 2001 and 2006. Pregnancy and neonatal outcomes were compared with a retrospective review of all 35 pregnancies (26 women) maintained on methadone in the same Swedish county, between 1982 and 2006. The authors reported no differences in pregnancy outcomes, however a significantly higher proportion of methadone-exposed infants had a birth weight <2500 gm (MM=25% vs. BM=6.4%; compared with a national Swedish average of 4.3%). Mean birth weight of the

methadone-exposed infants (2941±483 gm) was also significantly lower than the buprenorphine-exposed infants (3250±528 gm; $F[1,82]$ = 7.4, p = .008), however the difference was no longer statistically significant when adjusting for gestational age ($F[1,81]$ =3.4, p = .07). Significantly higher rates and severity of NAS was seen in the methadone-exposed group (Kakko, et al., 2008).

In a large prospective multicentre study, Lejeune et al. (2006) prospectively followed 260 infants born to women maintained on methadone (39%) or buprenorphine (61%) during pregnancy. Women were recruited consecutively from 35 French perinatal centres in public hospitals over a 12 month period. No significant differences in terms of maternal or neonatal outcomes were reported. Mean birth weight of the buprenorphine-exposed infants (2843 gm) was comparable to that of infants prenatally exposed to methadone (2790 gm) and there was a non-significant association between methadone-exposure and preterm delivery (16% of MM vs. 10% of BM). Forty six percent of methadone-exposed infants had a birth length <10[th]percentile, compared with 34% of infants prenatally exposed to buprenorphine. There was a seven percent increase in intrauterine growth retardation (IGR) for infants prenatally exposed to methadone, although this difference was not statistically significant. Fifty two percent of buprenorphine-exposed infants required treatment for NAS, compared with 49% of methadone-exposed infants, while the mean age at maximum NAS score was higher for the methadone-exposed infants (80 hr post-delivery) compared with the buprenorphine-exposed infants (66 hr post-delivery, p=.07) (Lejeune, et al., 2006).

In a well-controlled prospective study, Ebner et al. (2007) compared the neonatal outcomes of 22 infants prenatally exposed to methadone during pregnancy and 14 infants prenatally exposed to buprenorphine in Vienna, Austria. Women with illicit poly-substance abuse (self-reported or detected via urinalysis) in the third trimester or at delivery were excluded, as were women with alcohol or benzodiazepine co-dependence. The authors reported no significant difference in birth growth measurements or Apgar scores between infants prenatally exposed to methadone or

buprenorphine. Although infants prenatally exposed to buprenorphine had an earlier mean onset of NAS symptoms compared with the methadone-exposed infants (34 hr [*SD* ±5.3; range 25-52 hr] vs. 58 hr [*SD* ±37.5; range 16-161 hr] post-delivery), this difference was not statistically significant. A significantly greater proportion of methadone-exposed infants required pharmacological treatment for NAS symptoms (68% vs. 21%) compared with buprenorphine-exposed infants (Ebner, et al., 2007).

To date, three randomised, controlled, double-blind, flexible-dosing trials have been conducted to examine differences between women maintained on methadone and women maintained on buprenorphine during pregnancy, and their infants (Fischer, et al., 2006; Jones, et al., 2005; Jones, et al., 2010). The first two studies (Fischer, et al., 2006; Jones, et al., 2005) were limited by small subject numbers (*N*=14 and *N*=20, respectively) and thus had limited power to detect differences between the groups. However, Jones et al. (2005) found that infants prenatally exposed to buprenorphine had significantly shorter hospital stays compared with methadone-exposed infants (BM=6.8 days vs. MM=8.1 days, *p*=.02). Additionally, non-significant trends were observed in both studies suggesting slightly better outcomes for infants exposed to buprenorphine on a number of other measures. Jones and colleagues (2005) reported no differences between the BM (*n*=9) and MM (*n*=11) groups in terms of infants' gestation at delivery, Apgar scores, or NAS severity. They also reported that head circumference and length at birth were similar between the groups, although infants exposed to buprenorphine had a heavier mean weight at birth (3530±16.7 gm) than infants exposed to methadone (3001±120.7 gm). In this study, 22% of BM infants required treatment for NAS, compared with 46% of MM infants. Although mean peak NAS scores did not differ between the groups, the total amount of morphine solution (equivalent to morphine 0.02 mg/drop) administered to treat NAS was greater in the MM group (93.1±23.5 drops vs. BM=23.6±19.3 drops). Additionally, infants prenatally exposed to methadone had a significantly longer length of hospital stay than infants prenatally exposed to buprenorphine (MM=8.1±0.8 days; BM=6.8±0.9 days, *p*=.02) (Jones, et al., 2005).

Consistent with the findings of Jones et al. (2005), Fischer and colleagues (2006) reported no differences between the BM (*n*=8) and MM (*n*=6) groups in terms of infants' birth weight, gestation, Apgar scores, or NAS severity, however independent values for each group were not reported. The authors reported that 50% of the MM infants required treatment for NAS symptoms, compared to 63% of the BM infants, however, infants exposed to methadone required treatment an average of 12 hours earlier than infants exposed to buprenorphine (Fischer, et al., 2006).

In the largest randomised, controlled study to date, Jones et al. (2010) compared the neonatal outcomes for 131 infants born to women maintained on buprenorphine (*n*=58) and methadone (*n*=73) during pregnancy. The authors used the Bonferroni principle to set the family-wise alpha level (i.e. nominal alpha level, .05 divided by the number of outcome variables) at .0091 for the five primary neonatal outcome variables (i.e. proportion of infants treated for NAS, NAS peak score, total mg of morphine, duration of hospital stay, and HC at birth), and at .003125 for the 16 secondary outcome variables (e.g. birth weight, proportion of infants born preterm, gestational age at delivery, duration of NAS treatment, and maternal obstetric outcomes) (Jones, et al., 2010; Matsunaga, 2006). The groups did not differ significantly on the proportion of infants treated for NAS (BM= 47%, MM=57%, *p*=.26), peak NAS score (BM: *M±SE*= 11.0±0.6; MM: *M±SE*= 12.8±0.6, *p*=.04), or birth HC (BM: *M±SE*= 33.8±0.3 cm; MM: *M±SE*= 33.0±0.3 cm, *p*=.03), however compared with the BM group, MM infants had significantly poorer outcomes for the total amount of morphine required for treatment of NAS (BM: *M±SE*= 1.1±0.7 mg vs. MM: *M±SE*= 10.4±2.6, *p*<.0091), duration of NAS treatment (BM: *M±SE*= 4.1±1.0 days vs. MM: *M±SE*= 9.9±1.6, *p*<.003125), and duration of hospital stay (BM: *M±SE*= 10.0±1.2 days vs. MM: *M±SE*= 17.5±1.5, *p*<.0091). These differences remained after adjusting for length of time that the mother had been taking the study medication, maternal use of other substances during pregnancy, number of antenatal visits, and gestational age at delivery. Amount of morphine required for treatment of NAS and length of hospital stay remained significantly different between the groups (*p*<.001 and

p= .003, respectively) after maternal opioid dependence levels were taken into account. Infants in the BM group were also heavier at birth (*M±SE*= 3093.7±72. 6 gm) compared with the MM group (*M±SE*= 2878.5±66.3 gm, *p*=.03), and were born at a later gestation age (*M±SE*= 39.1±0.3 weeks vs. *M±SE*= 37.9±0.3, *p*=.007), although these differences were not considered statistically significant by the authors. The authors reported no differences between the groups in terms of maternal obstetric outcomes, although women randomised to receive buprenorphine were more likely to discontinue their participation in the study (BM= 28/86, 33%, MM=16/89, 18%, *p*=.02). It was concluded that buprenorphine was superior to methadone in terms of reducing NAS severity, in that infants prenatally exposed to buprenorphine required significantly less pharmaceutical treatment for NAS, required NAS treatment for a significantly shorter duration, and required a hospital stay of shorter duration than methadone exposed infants. The authors asserted that buprenorphine should be considered as a first line treatment for opioid dependence in pregnancy, but cautioned that patient satisfaction and adherence to treatment was an important consideration when prescribing buprenorphine as an alternative to methadone (Jones, et al., 2010).

Despite these positive outcomes for pregnant women and neonates exposed to buprenorphine *in utero*, buprenorphine has not yet been recommended for use during pregnancy, and methadone remains the gold standard of care for the treatment for pregnant women with opioid-dependence (Center for Substance Abuse Treatment, 2004; Lintzeris, et al., 2006). This is because the safety, efficacy and effectiveness of buprenorphine throughout pregnancy and the neonatal period has not yet been definitively established, and there is a paucity of data regarding longer term childhood outcomes (Lintzeris, et al., 2006). Research to date indicates that treatment with buprenorphine may offer advantages over methadone maintenance during pregnancy and the neonatal period in terms of low transplacental transfer, lower incidence and severity of NAS and, due to its poor oral bioavailability, less exposure to active medication through breast milk (R. E. Johnson, Jones, et al., 2003; Nanovskaya, Deshmukh, Brooks, & Ahmed, 2002).

1.9 Physical development after prenatal exposure to opioids

The opioid system is related to growth and development *in utero* and opioid receptors are found in the brain, spinal cord, as well as in various organ sites of the developing foetus (Farid, et al., 2008; Jaffe, et al., 1997). Opioid receptor expression is regulated by signals from growth factors and neurotransmitters, both of which are affected by prenatal exposure to opioids (Robinson, 2000, 2002; Tiong & Olley, 1988; Wu, Mo, Yabe, Schwartz, & Robinson, 2001). There is general agreement that prenatal exposure to illicit opioids can result in low birth weight, thought to be related to intrauterine growth restriction (IGR) (Farid, et al., 2008; Kandall, et al., 1976; Lifschitz, et al., 1983; Shankaran et al., 2007).

1.9.1 Physical development after prenatal exposure to methadone and/or heroin

The following section provides an overview of previous research examining physical development after prenatal exposure to methadone and/or heroin. First, animal studies are discussed, followed by human studies using retrospective case-note review or cross-sectional designs, then prospective longitudinal studies are reviewed.

Animal research has posited that low birth weight in opioid-exposed rat pups may be due to withdrawal *in utero.* Lichtblau and Sparber (1981) suggested that the once daily dosing regimen of methadone may result in the foetus undergoing withdrawal symptoms prior to each subsequent dose. In an experimental study (Lichtblau & Sparber, 1981) rat pups were prenatally exposed to 1 or 4 mg/kg of the long-acting derivative of methadone, ι-α-acetylmethadol (LAAM), administered once per day to pregnant females. In order to induce withdrawal in the foetus, 1 mg/kg of the opioid antagonist naloxone was administered to half of the sample, four and two hours prior to LAAM dosing. Results showed that whilst the birth weight and nose-to-tail length of pups prenatally exposed to LAAM did not differ significantly from non-exposed control pups, pups who were prenatally withdrawn from either dose of LAAM showed significantly reduced body weight and nose-to-tail length at birth compared with non-exposed pups. Additionally, pups prenatally

exposed to either dose of LAAM failed to gain weight postnatally. The authors suggested that restrictions in postnatal weight gain may be related to chronic intoxication, due to persisting opioid activity in the brain, which may suppress feeding and other behaviours required for healthy development (Lichtblau & Sparber, 1981).

In a more recent study, Hutchings et al. (1992) reported that higher maternal doses of methadone administered via constant infusion had a transient effect on postnatal growth of rat pups, with pups prenatally exposed to 15 mg/kg/day methadone showing initial deficits in weight gain, compared with pups prenatally exposed to 10 mg/kg/day methadone or a non-treated control group. The authors reported a catch-up effect by the 50th postnatal day but it was unclear whether delays in growth may have been secondary to NAS symptoms or a direct effect of methadone on infant growth (Hutchings, et al., 1992).

In a retrospective study of 266 infants prenatally exposed to heroin (*n*=61) methadone (*n*=106), or a combination of the two (*n*=59), Kandall et al. (1976) reported that the average birth weight of infants prenatally exposed to methadone alone (*M±SEM*=2961±52 gm) was significantly higher than the combined average birth weight of infants prenatally exposed to heroin (*M±SEM*=2490±87 gm), both heroin and methadone (*M±SEM*=2535±86 gm) and a group of 33 infants of drug-free ex-heroin users (*M±SEM*=2615±74 gm). This difference was not accounted for by gestational age. In addition, the authors found that the mean birth weight of 66 infants in a non-exposed comparison group had significantly higher birth weights (*M±SEM*=3176±64 gm) than infants in the methadone-only group (*M±SE*=2961±52 gm). When possible confounding factors were examined, it was found that although a lack of prenatal care was associated with poorer birth weight in all substance-exposed groups, infants prenatally exposed to methadone alone were significantly heavier than infants who had been exposed to heroin or both heroin and methadone, independent of the level of prenatal care received (Kandall, et al., 1976).

A Dutch cross-sectional study (van Baar, Fleury, Soepatmi, Ultee, & Wesselman, 1989) found that infants prenatally exposed to opioids (*n*=35; predominantly combinations of methadone and heroin) had a lower mean birth weight (*M±SD*=2880.8±415.3 gm) than a non-exposed comparison group (*n*=37; *M±SD*=3428.8±439.9 gm). These authors noted that there was a high rate of maternal cigarette smoking during pregnancy (100%) in the group of opioid-exposed infants, and over half of the infants had also been exposed to maternal cocaine use throughout pregnancy (van Baar, Fleury, Soepatmi, et al., 1989). The prevalence of maternal smoking was not reported for the comparison group in this study, neither was there a measure of prenatal care, and analyses of growth measures did not adjust for any of these potentially confounding variables.

An early prospective study compared the growth and development of 22 children prenatally exposed to heroin and that of a number of other groups of infants, including those considered to be (i) medically 'high-risk' (*n*=15), (ii) children raised in a 'drug environment' but with no prenatal exposure to any substance (*n*=20), and (iii) a group of children of similar socioeconomic background (*n*=20) (Wilson, et al., 1979). The children were born between 1968 and 1970 and were followed up in 1974. The mean birth weight of the heroin-exposed (*M*=2750 gm) and the medically 'high-risk' (*M*=2722 gm) infants was significantly lower than infants in either the drug environment (*M*=3090 gm) or the socioeconomic comparison (*M*=3317 gm; pooled *SD*=24.28, *p*<.05) groups. Mean one-minute Apgar scores of the heroin-exposed (*M*=7.8) and the medically high-risk (*M*=7.2) infants were significantly lower than infants in either the drug environment (*M*=8.3) or the socioeconomic comparison (*M*=8.9; pooled *SD*=1.62, *p*<.05) groups. Wilson et al.(1979) also reported that infants in the heroin-exposed group stayed in hospital for an average of 18.0 days post-delivery, while the high-risk group of infants had an average hospital stay of 11.3 days. This was in comparison to the infants in the drug-environment group who had an average hospital stay of 2.8 days, and the socioeconomic comparison group who were discharged, on average, 4.0 days after birth (pooled *SD*=11.48, *p*<.05). Fifty five percent of heroin-exposed infants were treated for NAS; however, no details about NAS severity or duration were reported

by the authors. Gestational ages of the four groups of infants were comparable. The authors noted that the women who used heroin during pregnancy had significantly fewer prenatal care visits; however, data for this variable was not presented and infant analyses were not adjusted for this covariate (Wilson, et al., 1979). The children were re-assessed when they were aged 3 years, 1 month to 6 years, 4 months (*M*=4 years, 7 months). Although no means or standard deviations were provided, the authors reported that, after adjusting for age, sex, race and socioeconomic status, children in the heroin-exposed group had lower mean growth percentiles for height, and significantly lower mean growth percentiles for weight, and head circumference (HC), than infants in the other three groups. Further, it was reported that at follow-up a greater proportion of children in the heroin-exposed group had height and HC measurements below the third percentile compared with children in the comparison groups (Height = 32% vs. 12%, HC = 14% vs. 2%) (Wilson, et al., 1979).

Lifschitz and colleagues (1983) followed the development of 22 heroin-exposed, 21 methadone-exposed and 28 non-exposed comparison infants from birth to three years of age. While the small sample size of this study limits the power to detect differences between the groups, the authors reported that, despite similar gestation periods (38.4 to 39.0 weeks), the birth weight of infants in the heroin-exposed (*M±SD*=2751±521 gm) and the methadone-exposed (*M±SD*=2882±490 gm) groups was significantly lower than infants in the non-exposed comparison group (*M±SD*=3354±471; *p*<.01). Length and HC at birth were also significantly smaller in the heroin-exposed (Length: *M±SD*=47.4±2.8 cm; HC: *M±SD*=33.0±1.7 cm) and the methadone-exposed (Length: *M±SD*=47.7±2.8 cm; HC: *M±SD*=33.2±1.7 cm) groups compared to the non-exposed comparison group (Length: *M±SD*=49.8±2.3 cm; HC: *M±SD*=34.7±1.3 cm). It was also found that the proportion of infants who were small-for-gestational age (SGA; birth weight <10th percentile) in the heroin-exposed group (23%) was larger than in the methadone-exposed group (14%), and significantly greater compared to the non-exposed group (4%). After adjusting for several confounding factors (i.e. gender, race, prenatal care, prenatal risk score, maternal weight gain

during pregnancy, maternal education and maternal smoking) birth length no longer differed

significantly between the three groups of infants (adjusted means not presented). The authors

reported that the majority of infants who were SGA at birth were of comparable length to the

other infants at six months of age (Lifschitz, et al., 1983). At three year follow-up the mean

weight, length and HC of the three groups did not differ significantly (weight: heroin

$M\pm SD$=14.5±2.8 kg, methadone $M\pm SD$=14.0±1.9 kg, comparison $M\pm SD$=14.3±1.7 kg; length: heroin

$M\pm SD$=93.1±3.2 cm, methadone $M\pm SD$ =91.8±3.0 cm, comparison $M\pm SD$=93.4±3.6 cm; HC: heroin

$M\pm SD$=49.5±1.1 cm, methadone $M\pm SD$=49.2±1.5 cm, comparison $M\pm SD$=49.8±1.6 cm). However,

when length at three-years of age was adjusted for birth length, race, parental height and

maternal smoking, the mean length of the methadone-exposed group (M=91.9 cm) was smaller

than that of the non-exposed comparison group (M=92.6 cm), and significantly smaller than that

of the heroin-exposed group (M=94.4 cm; pooled SD=2.8, p<.05) (Lifschitz, et al., 1983).

Further analysis of this cohort (Lifschitz, et al., 1985) showed that there was a deceleration in HC

in the first year of life for almost one quarter of infants prenatally exposed to methadone

compared with seven percent of non-exposed comparison children. A similar deceleration of HC

occurred for a quarter of the heroin-exposed children in the second year. Multiple regression

analyses found that post natal head growth was significantly associated with birth weight, level of

maternal intra-partum risk and racial background (Lifschitz, et al., 1985). The authors concluded

that the postnatal growth of children prenatally exposed to opioids did not differ significantly

from that of a comparably high-risk group of non-exposed infants when adjusting for confounding

factors (Lifschitz, et al., 1983, 1985).

Soepatmi (1994) described developmental outcomes for 91 infants prenatally exposed to

substances of dependence (including opioids and non-opioids), born between 1974 and 1983 in a

Dutch hospital. Relative to non-exposed infants born at the same hospital, a greater proportion of

infants prenatally exposed to substances had a birth weight <10th percentile (non-exposed= 10%

vs. exposed= 24%) and were born preterm (non-exposed=15% vs. exposed=24%). Data were not presented separately for opioid-exposed and non-opioid exposed infants (Soepatmi, 1994). Long-term follow-up data were available for 45 opioid-exposed (heroin and methadone) Caucasian-Dutch infants. At one month post-birth, and at two years of age, children prenatally exposed to opioids were significantly smaller, in terms of Dutch growth percentiles for weight, length and HC, than children in the general Dutch population. At the final follow-up assessment, in 1986 when children were aged between 3.5 and 12 years of age, growth percentiles for weight and HC of the opioid-exposed children were similar to the Dutch general population; however growth percentiles for length remained significantly lower (Soepatmi, 1994). All growth percentiles were expressed in mean growth classes, however, as no explanation of this measurement was given and standard deviations were not provided the implications of these findings are difficult to interpret. While it was concluded that the developmental outcome of children prenatally exposed to opioids was poor in comparison to non-exposed children and children in the general Dutch population, the author advised that further prospective studies were needed (Soepatmi, 1994).

Johnson and colleagues (H. L. Johnson, Glassman, Fiks, & Rosen, 1987, 1990; H. L. Johnson & Rosen, 1982; Rosen & Johnson, 1982) examined the growth and development of 62 methadone-exposed infants from birth to 36 months of age. Non-exposed infants from comparably high-risk backgrounds (n=32) were matched to the methadone-exposed infants for gender, gestational age and birth weight. The authors reported that a significantly greater proportion of methadone-exposed infants had birth HC below the third percentile when compared with the non-exposed infants. However, proportions, means and standard deviations were not reported (Rosen & Johnson, 1982). This cohort was followed up at 36 months of age and the authors reported that weight and height did not differ significantly between the methadone-exposed group (n=39) and the non-exposed comparison group (n=23). The authors reported that there were a significantly greater proportion of children in the methadone-exposed group with HC below the third percentile (H. L. Johnson, et al., 1987, 1990). However, as proportions, means and standard

deviations were not reported for any of the growth parameters, it is difficult to interpret these findings.

In an American study Hans (1989) compared the developmental outcome of a group of children prenatally exposed to methadone (*n*=30) to that of a group of non-exposed children (*n*=44) of comparable economic, maternal intellectual and racial background. He reported that the mean birth weight of the methadone-exposed infants (*M±SD*=2865±605 gm) was significantly lower than that of the non-exposed comparison group [*M±SD*=3236±395 gm; *t*(72)=3.15, *p*<.01]. At two years of age, children exposed to methadone were significantly shorter (*M±SD*=85.1±4.3 cm) than non-exposed children [*M±SD*=87.3±2.9 cm; *F*(1,70)=4.54, *p*<.05] and had significantly smaller mean HC (*M±SD*=48.5±1.4 cm) compared with the non-exposed children [*M±SD*=49.5±1.5 cm; *F*(1,70)=6.97, *p*<.05]. Effect sizes were small to medium (Pearson *eta* coefficients = .26 to .28) and all mean growth parameters were reportedly within the normal range (Hans, 1989). While it was noted that the majority of women in the methadone group had also used other substances (including alcohol, marijuana, heroin, cocaine and Valium®) during pregnancy, the author did not provide any further details regarding the proportion of women who had used these substances in addition to methadone, and pre-natal exposure to other substances was not controlled for in analyses.

In a recent Australian paper, Hunt and colleagues (2008) described a case control study following the development of 133 methadone-exposed infants and 103 non-exposed infants to three years of age. Twenty-four percent of the methadone-exposed infants were born preterm and 25% were SGA, the proportions for the non-exposed infants were not reported although, at birth, the mean growth measurements of the non-exposed infants (weight=3.3 kg, length=51.6 cm, and HC=34.5 cm) were significantly greater than those of the methadone-exposed group (weight =2.9 kg, length=49.6 cm, and HC=33.6cm). However, these differences were accounted for by the earlier

mean gestation of the methadone-exposed infants (*M*=37.7 weeks) compared with the non-exposed group (*M*=40.2 weeks). When the infants were assessed at 18 months and three years of age, the methadone-exposed group had caught up to the non-exposed group in terms of mean weight and HC. Hunt and colleagues reported that the methadone-exposed children remained significantly shorter (18 months *M*=81.0 cm, 3 years *M*=92.8 cm) than the non-exposed children (18 months *M*=82.4 cm, 3 years *M*=96.7 cm), after adjusting for gestation, maternal height and maternal smoking, with the difference in height increasing over time (Hunt, et al., 2008). However, the authors did not appear to adjust for any other potentially important covariates, including gestational age, maternal use of other substances, treatment for NAS, or other health and social factors, and no explanations for the obtained results were provided.

1.9.2 Physical development after prenatal exposure to buprenorphine

Animal studies have shown differing results in term of postnatal growth after prenatal exposure to buprenorphine. In an experimental study (Tiong & Olley, 1988) rat pups were prenatally exposed to 4 mg/kg or 8 mg/kg methadone, or 1 mg/kg or 2 mg/kg buprenorphine, administered once per day to pregnant dams. When mean litter size was compared, non-treated control dams produced significantly larger litters (*M±SEM*=9.7±0.6 pups), compared with dams receiving 4mg/kg methadone (*M±SEM*=7.6±0.8 pups, *p*<.05) and 2 mg/kg buprenorphine (*M±SEM*=7.4±1.2 pups, *p*<.05). Birth weight of pups was not reported. There was a significantly higher rate of death for pups exposed to buprenorphine, with 53% of the 1 mg/kg group and 65% of the 2 mg/kg group perishing by postnatal day five, compared with 2% of non-exposed controls, although the authors suggested that rejection of pups by foster mothers or pup viability may have contributed to this high rate of mortality. When pups were weighed on postnatal day 20, the buprenorphine-exposed groups weighed less than methadone-exposed and control pups, however this difference was not statistically significant (Tiong & Olley, 1988). The authors cautioned that the adverse events observed in the neonatal rat pups may have been related to the regimen of a once daily injection of buprenorphine to the pregnant females. It was explained that rats metabolise opioids

more rapidly than do humans, and the fluctuations in drug levels may have exposed the developing foetus to withdrawal, with subsequent harmful effects (Tiong & Olley, 1988).

Research by Hutchings, Zmitrovich, Hamowy and Liu (1995) found no differences in birth weight or postnatal growth (to postnatal day 60) between male rat pups prenatally exposed to differing amounts of buprenorphine (0.3 mg, 1 mg, or 3 mg/kg/day), sterile water (both administered via constant infusion), and those in a non-treated group (Hutchings, et al., 1995). However, female pups prenatally exposed to 3 mg/kg/day buprenorphine demonstrated a significant decrease in body weight at postnatal day 30, compared to the pups prenatally exposed to sterile water and 1 mg/kg/day buprenorphine. This difference was not observed at any other time. The authors suggested that fewer toxic effects have been found with the administration of medication via constant infusion, thus eliminating daily peak drug concentrations (Hutchings, et al., 1995), as opposed to the once per day dosing as described in Tiong and Olley's study (1988).

In terms of studies examining growth outcomes, beyond the neonatal period, for human infants prenatally exposed to buprenorphine, Schindler et al. (2003) described the development of four infants born to two women maintained on buprenorphine during pregnancy. Both women had been inducted onto buprenorphine during the second trimester of their first pregnancy and had conceived their second infant whilst receiving buprenorphine maintenance therapy. It was reported that all infants were born at term, had high Apgar scores (9 to 10) and birth measurements within normal limits (weight=2800 to 3430 gm; length=49 to 51 cm; HC=33 to 35 cm). While no long term data was presented, according to the authors, the longer term development of all four children was comparable to non-exposed children (Schindler, et al., 2003). Retrospective case-note review of 13 infants exposed to buprenorphine in pregnancy was reported by Kayemba-Kay's and Laclyde (2003). In this sample the majority of infants (12/13) were born at term (one infant was born at 36 weeks gestation, overall M=39 weeks gestation). Two infants had a birth weight ≤2500 gm (overall M=3000 gm), four infants were SGA, Apgar

scores for all infants were within the normal range (data not provided) and 77% of cases required

pharmacological treatment for symptoms of NAS. Length of hospital stay ranged from 6 to 48

days post delivery. Although the authors reported that milestone acquisitions for the majority of

infants were within normal limits, no long term growth data were presented (Kayemba-Kay's &

Laclyde, 2003). A recent study by Sandtorv et al. (2009) followed the development of 15 infants

prenatally exposed to methadone (n=11) or buprenorphine (n=4) born in a Norwegian hospital

between 1999 and 2005. The authors reported that 10 of the infants were born at term, with two

sets of twins and one singleton delivered prior to 36 weeks gestation (overall M=39 weeks

gestation). The mean birth weight was 3102 gm and mean HC at birth was 34.1 cm. Three of the

four buprenorphine-exposed infants and all of the methadone exposed infants experienced NAS.

Two buprenorphine-exposed infants and eight methadone-exposed infants were treated

pharmacologically with morphine. The mean length of hospital stay was 27.4 days post delivery

(range 6-88 days). While it was reported that infant development was followed up to a mean age

of 30 months, no growth measurements were provided. Further, outcomes for the methadone

and buprenorphine exposed infants were not reported separately for many variables (Sandtorv,

et al., 2009).

1.10 Neurodevelopment after prenatal exposure to opioids

Early evaluation of neurological sequelae related to prenatal exposure to substances is

problematic because task-based assessment of neurological development is difficult with pre-

verbal children. Standardised tests are valuable in providing clinical assessments, however

they often rely on attention, motivation and learning, all three of which can affect results of

testing in infants (Moskowitz & Sokol, 1983).

Neurophysiologic techniques, such as visual evoked potentials (VEP) record electrographic

patterns which can be employed to assess brain development and maturation of visual

functioning (Scher et al., 1998). VEP tests the integrity of the visual pathway and provides

information about neural maturity by measuring the change in electrical potential within the

primary visual cortex in response to a visual stimulus (Cibis & Fitzgerald, 1993). Many studies

of visual system maturation have used diffuse flashes of light as the stimulus and it is

recognised that the latency of the flash VEP (FVEP) decreases with age (Moskowitz & Sokol,

1983). More recently pattern-reversal stimuli (PVEP) has been used to measure visual

maturity in infants as it is known to show less inter- and intrapersonal variability in measures

of latency in normal infants. It is also more sensitive than FVEP to visual pathway lesions (Aso

et al., 1988). An advantage of assessment using VEP is that from as early as a few weeks of

age, changes are evident in the development of mechanisms fundamental to the maturation

of visual functioning (Moskowitz & Sokol, 1983). Abnormal responses (including prolonged

latencies) may be a sign of neurological immaturity and reflect neurophysiologic dysfunction

in otherwise asymptomatic infants (Hansen, Struthers, & Gospe, 1993; McCulloch, Orbach, &

Skarf, 1999; Scher, et al., 1998). A decrease in latency to the first major positive component

(P1) elicited through VEP is a reliable index of visual maturation, predominantly associated

with myelination of the optic nerve (Algarin, Peirano, Garrido, Pizarro, & Lozoff, 2003; Aso, et

al., 1988; Hansen, et al., 1993; Pinto, Onofrj, Pola, Tempesta, & Torrioli, 1986).

1.10.1 Visual Evoked Potentials after prenatal exposure to methadone

Delays in both P1 and N75 (the first major positive and negative components of the VEP

waveform) latencies were reported by Bauer (1998) who found that adults maintained on

methadone (*n*=22) exhibited significantly slower latencies than non-drug using adults (*n*=21) and a

group of adults with past history of heroin dependence, but no current use (*n*=37). There was a

significant relationship between the severity of heroin use (i.e. years used) and the N75 latency

response; however this relationship was not evident for the P1 latency response. Bauer found no

correlation between latencies and either duration of abstinence from heroin or methadone blood

levels. It was concluded that delayed latencies were best accounted for by accumulated effects of

chronic opioid dependence (L. O. Bauer, 1998). Alterations in P1 latencies of rat pups prenatally

exposed to high doses of methadone have also been observed at the peak of NAS, however they returned to normal by 21 days of age (Pinto, et al., 1986). Abnormal responses to VEP (including absent or delayed latencies) in children prenatally exposed to cocaine, cannabis, alcohol and nicotine have also been reported (Dixon, Coen, & Crutchfield, 1987; Olegard et al., 1979; Scher, et al., 1998; Tansley, Fried, & Mount, 1986).

A very early study compared VEP responses of infants prenatally exposed to methadone and/or heroin (n=15) to those of non-exposed control infants (n=10) (Lodge, Marcus, & Ramer, 1975). It was reported VEPs of newborn infants prenatally exposed to narcotics were irregular and less reliable than those of the non-exposed newborn infants. Exposed infants also showed poorer levels of arousal and attentiveness than the non-exposed infants (Lodge, et al., 1975). A recent study found that amplitudes of flash VEP were small and of poorer quality in infants prenatally exposed to methadone and illicit opioids (n=21) compared to non-exposed infants (n=20) (McCulloch et al., 2007; McGlone et al., 2008). When tested at one to four days of age, a greater proportion of MM exposed infants (>50%) had abnormal waveforms that were significantly smaller in amplitude than those of the non-exposed infants (MM: median 10.6 mV, range 0–30; non-exposed: median 24.4 mV, range 8–69). Median amplitude of VEPs remained smaller for MM-exposed infants when re-tested after one week. The authors noted that, compared with the non-exposed infants, the MM-exposed infants were significantly smaller at birth (2818 gm vs. 3486 gm; p<.01), had significantly smaller occipito-frontal circumferences (32.9 cm vs. 34.9 cm; p<.01), and were born at a significantly earlier gestation ($M\pm SD$=38.6±1.4 vs. $M\pm SD$=39.8±0.95 weeks, p<.01). Over half of the MM mothers had used benzodiazepines whilst pregnant; however, because of the small sample size it was not possible to adjust for the effects of potential confounders (McGlone, et al., 2008). Mulvihill and colleagues (2007) described ophthalmic examinations of children prenatally exposed to opiates and/or benzodiazepines (n=14). Children were recruited if they had a diagnosis of horizontal nystagmus. Seven children reportedly had delays in visual functioning, although details of testing were not provided. Three children were

examined using VEP (two were aged four years and one was aged eight years at testing). The authors reported that all three children had normal responses to VEP; however neither data nor details of the VEP testing were provided (Mulvihill, et al., 2007).

Most recently Hamilton et al. (2010) presented a retrospective case review of children prenatally exposed to methadone maintenance (*n*=20). Responses to flash, pattern-reversal and pattern onset VEPs were recorded, with age at assessment ranging from three months to seven years. The authors reported delayed responses to flash VEP in 3/11 children, delay or absence of response to pattern-reversal VEP was seen in 4/6 children, whilst 1/6 children had a delayed response to a pattern onset VEP. One child had a delayed or absent response to all three VEP assessments, although no abnormality in MRI was observed for this child. In the majority of cases, delayed or absent responses to VEPs were associated with a history of pharmacological treatment for NAS and the presence of nystagmus. Whilst the authors noted that over half of the children in the study had been exposed to benzodiazepines or heroin *in utero,* in addition to MM, the sample was too small to separate the individual effects of these substances on VEP responses (Hamilton, et al., 2010).

1.10.2 Cognitive Development after prenatal exposure to methadone and/or heroin
It is unclear whether children prenatally exposed to opioids are at greater risk than non-exposed children of longer term cognitive problems. Whilst some researchers have reported adverse outcomes for children prenatally exposed to either illicit heroin use or prescribed methadone maintenance (Davis & Templer, 1988; Hunt, et al., 2008; van Baar & de Graaff, 1994), others have reported no longer term developmental problems (Kaltenbach & Finnegan, 1987; Wilson, 1989). There is a paucity of research examining children's cognitive development longitudinally, and many studies have not compared outcomes with those of non-exposed infants, have had small samples, or poor follow-up rates.

In a cross-sectional study, Davis and Templer (1988) compared the neuropsychological status of children who were exposed to opioids (heroin and/or methadone, n=28) in pregnancy, with a group of reference children (n=28) who were not prenatally exposed to opioids but who resided with a father figure with an opioid-addiction. Children were aged between six and 15 years at assessment. Mean age at assessment was significantly lower for the narcotic-exposed children than the non-exposed children (M±SD=8.50±2.52 vs. M±SD=11.21±2.96 years, p<.001), and age was used as a covariate in analyses. Opioid-exposed children scored significantly lower than non-exposed children on the Wechsler Intelligence Scale for Children - Revised (WISC-R) Full Scale (M±SD =90.36±11.36 vs. M±SD =96.32±8.72, F=5.03, p<.05) and Performance IQ scores (M±SD=88.21±17.33 vs. M±SD=100.00±9.82, F=5.95, p<.05). Mean scores for Verbal IQ did not differ significantly between the groups. When results were examined at the subtest level, opioid-exposed children performed more poorly on subtests that examined perception, attention and motor skills (Digit Span: M±SD=8.04±2.81 vs. M±SD=9.29±2.79, F=5.37, p<.05; Picture Completion: M±SD=8.54±2.08 vs. M±SD=10.21±2.28, F=7.16, p<.01; Object Assembly: M±SD=9.00±2.19 vs. M±SD=10.39±1.99, F=6.21, p<.05; Coding: M±SD=8.11±3.07 vs. M±SD=10.42±3.08, F=5.35, p<.05). Opioid-exposed children also achieved significantly higher mean scores (indicating poorer performance) than the non-exposed children, on the neurological indicators of the Bender-Gestalt Test (M±SD=6.95±3.42 vs. M±SD=2.54±2.00, p<.001) (Davis & Templer, 1988). Results were examined separately for a group of children who were prenatally exposed to only heroin (n=9), and a group who were exposed to only methadone (n=12). The methadone-exposed children scored more poorly than the heroin exposed children on the Information subtest of the WISC-R (M±SD=5.33±2.15 vs. M±SD=8.11±2.89, F=-2.53, p<.05), and achieved significantly higher scores (indicating poorer performance) than the heroin-exposed children on the Handwriting Skill subtest of the Quick Neurological Screening Test (M±SD=1.08±1.08 vs. M±SD=0.11±0.33, t=2.58, p<.05). No other significant differences were observed (Davis & Templer, 1988).

One of the earliest longitudinal studies followed the development of infants born to women participating in methadone maintenance (MM) in San Francisco (*n*=34), from birth to two years of age (Lodge, et al., 1975; Ramer & Lodge, 1975). Infants were assessed on the Bayley Scales of Infant Development (BSID) at three monthly intervals in the first year of life, and then at six monthly intervals thereafter. Preliminary BSID data were presented for six assessments (with *n*'s at each assessment ranging from 4 to 20). Mean scores for the Mental Developmental Index (MDI) ranged from low average (*M±SD*=89.80±10.94) to high average (*M±SD*=117.30±16.56); whilst mean scores for the Psychomotor Developmental Index (PDI) ranged from average (*M±SD*=105.71±14.65) to high average (*M±SD*=136.29±19.20). It was noted that MM-exposed infants appeared to show strengths in the areas of vocalisation and language development, but performed poorly on tasks requiring perceptual motor skills (Ramer & Lodge, 1975). A further study by the same research group included data from 88% of this sample (Lodge, et al., 1975). When tested on the BSID at one-month of age, MDI scores of 29 infants prenatally exposed to heroin and/or methadone were lower (*M±SD*=90.41±13.06) than scores of 10 non-exposed infants (*M±SD*=96.60±10.11). The authors suggested that the lower scores of the opiate-exposed infants were due to poorer orientation and less attentiveness to visual tasks. Mean scores on the Psychomotor Developmental Index (PDI) were found to be above average for both the opiate-exposed (*M±SD*=121.30±18.89) and the non-exposed (*M±SD*=126.60±14.14) infants (Lodge, et al., 1975).

In a prospective study, Wilson and colleagues (1979) compared the developmental outcomes of preschool children prenatally exposed to heroin (*n*=22) to those of (i) non-exposed children raised in a 'drug environment'(*n*=20), (ii) children deemed to be 'at risk' due to medical factors (*n*=15), and (iii) children from a similar socioeconomic background (*n*=20). The children were born between 1968 and 1970 and were followed up in 1974 (mean age at follow-up = 4 years, 7 months). The groups did not differ in mean age, gender, race, or socioeconomic status (SES). At follow-up, the heroin-exposed children were found to perform significantly more poorly on the

McCarthy Scales of Children's Abilities (McCarthy General Cognitive Index: M=88.71) than infants in the drug environment (M=92.87), the medically 'high-risk' (M=93.08), and the socioeconomic comparison (M=97.42; pooled SD=14.62, p<.05) groups. Mean Columbia Mental Maturity Scale Intellectual Quotient (IQ) scores were lower (but not significantly different) for the heroin-exposed children (M=96.06), when compared with the other three groups (drug environment: M=99.15; 'high-risk': M=100.51; socioeconomic comparison: M=99.48; pooled SD=13.44). The authors noted that whilst mean scores for the heroin-exposed group were consistently lower than those of the comparison groups, the majority of scores fell within the average range (Wilson, et al., 1979).

A further study by this research group followed the development of 29 heroin-exposed infants, 39 methadone-exposed infants and 57 non-exposed comparison infants (Wilson, 1989; Wilson, et al., 1981). The authors reported that groups were matched for maternal age, race, SES, marital status, and gestational age at the commencement of prenatal care, however matching criteria were not provided. Information on the infants' medical, neurological, social and behavioural development was collected at six weeks of age, at three monthly intervals during the first year of life, at 18 and 24 months of age, then annually until the children were at preschool. Mean scores on the BSID and McCarthy Scales were within the normal range and did not differ significantly between the groups. The exceptions to this were a significant delay in psychomotor development reported for nine-month old infants prenatally exposed to methadone ($M\pm SD$=89.9±12.6) compared with children in the non-exposed comparison group ($M\pm SD$=99.0±14.5; p<.01), and significant delays in cognitive function reported for 18-month old children prenatally exposed to heroin (MDI: $M\pm SD$=86.5±10.7) compared with children in the non-exposed comparison group ($M\pm SD$=97.4±14.4; p<.01) (Wilson, 1989; Wilson, et al., 1981). No significant differences in MDI performance were reported for the methadone-exposed group at the 18-month assessment ($M\pm SD$=92.0±14.5), and cognitive function of all three groups was comparable at 24 months of age. The cognitive developmental scores for the heroin-exposed group were noted to fluctuate

between assessments, and scores for all three groups of children were noted to decline over time. A phenomenon that the authors attributed to the level of disadvantage experienced by this study population and particularly the poor home environments of the drug-exposed children (Wilson, 1989).

This same group of children were assessed using the McCarthy Scales of Children's Abilities between three and five years of age (mean age at testing = three years, five months) (Lifschitz, et al., 1985). Mean McCarthy General Cognitive Index (GCI) scores did not differ significantly between the three groups of children, although the authors suggested that it was of clinical importance that a higher proportion of heroin-exposed infants scored within the 'mildly retarded' range compared with the non-exposed infants (20% vs. 2%). Multiple regression analyses showed that amount of prenatal care, level of prenatal risk, and quality of the child's home environment were the best predictors of GCI score (Lifschitz, et al., 1985; Wilson, 1989).

In another American study, Johnson et al. (H. L. Johnson, et al., 1987, 1990; H. L. Johnson & Rosen, 1982; Rosen & Johnson, 1982) compared the development of children prenatally exposed to methadone (*n*=62) with non-exposed infants from comparably high-risk backgrounds (*n*=32). At six months of age mean scores on the MDI and PDI of the BSID were lower for infants prenatally exposed to methadone (MDI: *M±SD*=95.8±16.1; PDI: *M±SD*=101.0±18.2) than for the comparison group (MDI: *M±SD*=100.7±20.1; PDI: *M±SD*=105.1±14.2), however the authors commented that the differences did not reach statistical significance due to large within-group variance (H. L. Johnson & Rosen, 1982). Additionally, lower BSID scores were significantly associated with abnormal neurological signs for the methadone-exposed infants. A greater frequency of low scores (< 85, or 1 SD below the mean) was observed in the methadone-exposed group, with 20% of methadone-exposed infants scoring <85 on the MDI, compared with 17% of the non-exposed infants. A significantly greater proportion of methadone-exposed infants (15%) scored <85 on the PDI, compared with infants in the non-exposed group (8%, *p*<.01). When the distribution of low

scores across the two groups was examined for males and females separately, no significant differences were found for females infants, however male methadone-exposed infants were significantly more likely to score <85 on both the MDI (25%) and PDI (20%), compared with their non-exposed male peers (0%, $p<.05$ for both MDI and PDI) (H. L. Johnson & Rosen, 1982).

A subset of these children was followed up until 36 months of age (H. L. Johnson, et al., 1987, 1990; Rosen & Johnson, 1982). All mean scores fell within normal limits, however, at 12 months of age infants prenatally exposed to methadone (n =41) achieved significantly lower mean scores than comparison infants (n =22) on both the MDI ($M \pm SD$=98.37±2.68 vs. $M \pm SD$=107.00±2.81, $p<.05$) and the PDI ($M \pm SD$=94.93±2.53 vs. $M \pm SD$=102.78±2.30, $p<.05$). The authors noted that the gap in BSID scores between the two groups of infants widened over the course of the study, and at 18 months of age infants prenatally exposed to methadone (n =38) achieved significantly lower mean scores than comparison infants (n =23) on both the MDI ($M \pm SD$=96.00±2.31 vs. $M \pm SD$=106.38±3.56, $p<.05$) and the PDI ($M \pm SD$=92.62±2.38 vs. $M \pm SD$=105.29±2.21, $p<.05$) (Rosen & Johnson, 1982). At 36 months of age the two groups of infants did not differ significantly on scores or percentiles of the Merrill-Palmer Scale of Mental Tests (H. L. Johnson, et al., 1987, 1990).

Chasnoff and colleagues (Chasnoff, Hatcher, & Burns, 1982; Chasnoff, Schnoll, Burns, & Burns, 1984) compared the development of infants prenatally exposed to methadone (n=39), to that of poly-drug exposed infants (i.e. combinations of benzodiazepines, marijuana and other illicit substances, n=19) and non-exposed infants (n=27). When assessed with the BSID at 3, 6, 12 and 24 months of age, mean MDI and PDI scores for all three groups of children were within the normal range. There was a decline in mean scores between the 12 and 24 month assessments for all groups of children, which was attributed to low levels of SES and maternal education. The authors suggested that infants' long term development appeared to be related to these environmental factors rather than prenatal substance exposure. A limitation of this study was that

there was a high rate of attrition with nearly two thirds of the sample lost to follow-up over the study period (Chasnoff, et al., 1984).

A further study by this research group (Chasnoff, 1985; Chasnoff, Burns, Burns, & Schnoll, 1986) reported that, at six months of age, infants prenatally exposed to opioids (heroin, methadone and other illicitly used opioids, *n* =26) had significantly lower mean scores than non-exposed comparison infants (*n* =29) on the MDI (*M±SD*=103.6±13.5 vs. *M±SD*=111.0±12.3, *p*<.05). Twelve-month mean MDI scores were significantly lower for opioid-exposed infants (*n* =20, *M±SD*=99.6±10.6) than for non-exposed controls (*n* =27, *M±SD*=105.8±8.1, *p*<.05). Assessment at 24 months of age showed no significant differences in MDI or PDI scores, however, a slight decline in scores was observed for all groups of infants over time. As in their earlier research, there was a high rate of participant attrition over the course of assessments with over 50% of the sample lost to follow-up (Chasnoff, 1985; Chasnoff, et al., 1986).

Hans and colleagues (Bernstein & Hans, 1994; Hans, 1989; Huntington, Hans, & Zesking, 1990) followed 30 methadone-exposed infants from birth to 24 months of age and compared their development to that of 44 non-drug exposed infants. Groups were comparable in terms of maternal IQ, years of education, single parent status, race and SES. At two years of age, infants exposed to methadone had significantly lower PDI scores on the BSID than the non-exposed infants (*M±SD*=100.8±12.6 vs. *M±SD*=108.5±14.6, *F*(1,70)=5.19, *p*<.05, *eta*=.26). Methadone-exposed infants also scored significantly higher (indicating poorer functioning) on several of the BSID Infant Behaviour Record (IBR) items than their non-exposed peers. These were IBR tension (*M±SD*=4.3±0.8 vs. *M±SD*=4.0±0.6, *F*(1,70)=5.54, *p*<.05, *eta*=.26), IBR gross motor coordination (*M±SD*=26.±0.8 vs. *M±SD*=2.2±0.7, *F*(1,70)=6.08, *p*<.05, *eta*=.28), and IBR fine motor coordination (*M±SD*=2.8±0.6 vs. *M±SD*=2.5±0.7, *F*(1,70)=4.29, *p*<.05, *eta*=.24). It was noted that mean scores for these outcomes were well within the average range (Hans, 1989). Mean scores on the MDI were in the average range and did not differ significantly between methadone-exposed and

comparison children. However, when the children from very low SES families were examined

separately (n not provided), the methadone-exposed infants scored more poorly than the non-

exposed infants on the MDI (M=86 vs. M=97, eta=.41). While methadone-exposed infants also

performed more poorly on the PDI than the non-exposed children (M=98 vs. M=104), the effect of

substance-exposure was not as large (eta=.21). Additionally, methadone-exposed infants from

low SES backgrounds scored more poorly on the IBR items than non-exposed infants. It was

concluded that prenatal exposure to methadone may increase susceptibility to the effects of a

disadvantaged environment (Hans, 1989).

In further research, these authors explored the relative contribution of social-environmental risks

to the developmental outcomes of the same group of children and found that substance-

exposure alone did not predict poorer developmental outcome. Further, the authors discovered

that individual and cumulative risk factors (e.g. maternal IQ, level of maternal psychosocial stress,

parent-child interaction), independent of prenatal exposure to methadone, predicted

developmental outcome for methadone-exposed children at only the extremes of the risk

continuum (Bernstein & Hans, 1994).

In a Dutch longitudinal study, van Baar et al. described the cognitive development of 35 children

prenatally exposed to methadone maintenance as well as other substances (including heroin and

cocaine), to that of a group of 37 children who were not exposed to substances in pregnancy (van

Baar, 1990; van Baar & de Graaff, 1994; van Baar, Fleury, & Ultee, 1989; van Baar, Soepatmi,

Gunning, & Akkerhuis, 1994). Children were assessed at six monthly intervals from six to 30

months of age on a Dutch version of the BSID, and then yearly to five and a half years of age on

Dutch intelligence tests. Mean scores on the PDI of the BSID were all within the average range and

did not differ significantly between the groups at any of the assessments. There were no

significant differences between the groups for mean MDI scores at 6, 12 and 18 months of age,

and all mean scores were within the average range. However, at 24 and 30 months of age, the

substance-exposed children scored significantly more poorly than the non-exposed children on the MDI [24 months: $M\pm SD$=86±15 vs. $M\pm SD$=98±16, t(58)=2.98, p<.01; 30 months: $M\pm SD$=87±18 vs. $M\pm SD$=101±20, t(57)=2.68, p<.01]. At the 24 month assessment, a greater proportion of substance-exposed children scored <84 (1 SD below the mean), on the MDI (n=12/26, 46%), compared with the non-exposed children (n=8/34, 24%). This was also the case with the 30 month assessment where 36% (n=9/25) of the substance-exposed children scored 1 SD below the mean, compared with 15% (n=5/34) of the non-exposed group (van Baar, 1990; van Baar, Fleury, & Ultee, 1989; van Baar, et al., 1994).

Testing at later ages showed that the substance-exposed children continued to perform significantly more poorly on measures of general intelligence and language development, in comparison to their non-exposed peers. When assessed at three and a half years of age, children prenatally exposed to substances had significantly lower mean scores on the Snijders-Oomen Nonverbal (SON) intelligence test IQ scale than their non-exposed peers ($M\pm SD$=99±9 vs. $M\pm SD$=109±11, t(53)=3.75, p<.01). Similarly, mean scores on the Revision of the Amsterdam Children's Intelligence Test (RAKIT) IQ scale were significantly lower for substance-exposed children, compared with the non-exposed group, when assessed at four and a half, and five and a half years of age (4 ½ years: $M\pm SD$=85±11 vs. $M\pm SD$=103±15, t(52)=4.98, p<.01; 5 ½ years: $M\pm SD$=90±12 vs. $M\pm SD$=102±17, t(50)=2.61, p<.05). For the latter two of these assessments, a greater proportion of substance-exposed children scored <84 (1 SD below the mean), on the RAKIT (4 ½ years: n=14/23, 61%; 5 ½ years: n=9/22, 41%), compared with the non-exposed children (4 ½ years: n=5/31, 16%; 5 ½ years: n=4/30, 13%) (van Baar & de Graaff, 1994). Substance-exposed children were also found to have significant difficulties with language development when tested at four years of age on the Dutch version of the Reynell Developmental Language Scales, with the substance-exposed children performing significantly more poorly than the non-exposed children on both the Language Comprehension ($M\pm SD$=46±6 vs. $M\pm SD$=52±6, t(56)=4.32, p<.01), and the Language Expression ($M\pm SD$=46±9 vs. $M\pm SD$=50±6, t(55)=2.00, p<.05)

Scales (van Baar & de Graaff, 1994). A limitation of this longitudinal study was that 63% of the substance-exposed group were prenatally exposed to other substances (i.e. cocaine, tranquillisers and amphetamines) along with opioids. Two children (6%) were exposed to methadone only, whilst 31% were exposed to both heroin and methadone. It is therefore possible that the significant developmental deficits observed in the substance-exposed group may have been related to their exposure to substances other than opioids.

In a large American prospective, longitudinal, multi-site study, Messinger and colleagues (2004) administered the Bayley Scales of Infant Development- Second Edition (BSID-II) to a large number of infants (n=1227) at one, two and three years of age. The infants were divided into four groups (i) infants prenatally exposed to cocaine only (n=474), (ii) infants who were prenatally exposed to opioids only (n=50), (iii) infants who were exposed to both cocaine and opioids (n=48), and (iv) infants who were not exposed to either substance (n=655). Mean BSID-II scores of infants who were exposed to opioids (n=98) were compared to those of infants who were not opioid-exposed (n=1129). At one year of age opioid-exposed children (n=79) scored significantly more poorly than the non opioid-exposed children (n=960) on the MDI at ($M\pm SD$=88.5±1.2 vs. $M\pm SD$=91.6±0.4, p<.05). Mean MDI scores at two and three years of age did not differ significantly between the two groups. Overall performance on the MDI (measured using an intercept term in a hierarchical linear model) was not associated with prenatal exposure to opioids (Messinger, et al., 2004). Opioid exposure was associated with significantly poorer PDI mean scores at two and three years of age (2 years: $M\pm SD$=89.0±1.7, n =79 vs. $M\pm SD$=95.2±0.5 n=859, p<.01; 3 years: $M\pm SD$=89.2±1.6, n=75 vs. $M\pm SD$=93.4±0.5, n=859, p<.05), and significantly poorer BRS mean scores at two years of age ($M\pm SD$=34.4±3.1, n=80 vs. $M\pm SD$=41.9±1.0, n=925, p<.05). Overall performance on the PDI was significantly associated with opioid exposure, with opioid-exposed children scoring 3.9 PDI points below non-opioid exposed children (p<.01). However, when analyses were adjusted for data collection site, infant age, ethnicity, birth weight, infants' home environment, and maternal care, no significant effect of opioid exposure remained. Overall performance on the BRS was not

associated with prenatal exposure to opioids (Messinger, et al., 2004). While it must be noted that the authors pooled these groups of infants for the purposes of the analyses (i.e. the non-opioid exposed group consisted of the 655 non-exposed infants as well as the 474 infants prenatally exposed to cocaine only), the opioid-cocaine exposure interaction effect was not statistically significant for any of the BSID-II analyses (Messinger, et al., 2004).

Hunt and colleagues (2008) followed the development of a group of methadone-exposed infants and a non-exposed group of infants in Sydney, Australia between 1979 and 1984. When assessed on the BSID at 18 months of age, scores for both groups of infants were in the normal range of development, although the methadone-exposed infants (n=79) were found to score significantly more poorly on the MDI ($M \pm SD$=88.2±16.4) than non-exposed infants (n=61, $M \pm SD$=105.0±23.0, p<.001). At three years of age methadone-exposed infants (n=67) were found to score significantly more poorly than the non-exposed infants (n=44) on the Stanford-Binet Intelligence Scale ($M \pm SD$=99.9±15.1 vs. $M \pm SD$=107.5±13.4, p<.01), the McCarthy Motor Scale ($M \pm SD$=49.5±8.7 vs. $M \pm SD$=53.9±8.3, p<.05), and the Reynell Expressive Language ($M \pm SD$=35.5±7.9 vs. $M \pm SD$=42.8±12.6, p<.05) and Verbal Comprehension scales ($M \pm SD$=42.4±11.6 vs. $M \pm SD$=49.2±11.4, p<.05). Mean scores of both groups were within the average range for all scales (Hunt, et al., 2008). Although this research mentioned significant differences between the two groups of infants in terms of infant growth and stability of primary carer, these covariates were not included in analyses. Neither was there any inclusion of other potentially important covariates such as gestational age, maternal use of other substances, treatment for NAS, or other health and social factors.

1.10.3 Neurodevelopment after prenatal exposure to buprenorphine

Only five studies have described the neurodevelopmental outcome of human infants prenatally exposed to buprenorphine (Kahila, Kivitie-Kallio, Halmesmaki, Valanne, & Autti, 2007; Kayemba-Kay's & Laclyde, 2003; Salo et al., 2009; Sandtorv, et al., 2009; Schindler, et al., 2003). Schindler et

al. (2003) described the pregnancy and early neonatal development of two infants conceived whilst their mothers were maintained on buprenorphine. It was reported that both infants had normal neurodevelopmental outcomes on clinical examination at six and 12 months of age (Schindler, et al., 2003). However, the details of the examinations were not included in the publication.

Retrospective case-note review of 13 infants exposed to buprenorphine in pregnancy was reported by Kayemba-Kay's et al. (2003). No anomalies were found in the reviewed electroencephalogram (EEG) recordings or cranial ultrasounds; however 54% of infants presented with transient hypertonia on clinical examination. In the majority of cases this resolved and developmental outcome at six and nine months, assessed using the Denver Developmental Screening Test, was considered within normal limits for 11 of the 13 infants (Kayemba-Kay's & Laclyde, 2003). However, no details of the test scores were provided in the publication. The authors suggested that future studies examining the longer term neurodevelopment of infants prenatally exposed to buprenorphine were needed (Kayemba-Kay's & Laclyde, 2003).

Kahila et al. (2007) undertook magnetic resonance imaging (MRI) scans of seven infants prenatally exposed to buprenorphine. All infants were assessed before two months of age. Visual examination of brain scans found no structural anomalies and no evidence of irregular MRI signal intensity. The authors concluded that buprenorphine maintenance therapy did not cause hypoxic-ischemic brain changes to exposed infants. The need for further studies examining the brain development of children exposed to buprenorphine was acknowledged by the authors (Kahila, Kivitie-Kallio, et al., 2007).

Sandtorv et al. (2009) described the development of 15 infants prenatally exposed to methadone (n=11) or buprenorphine (n=4) in Norway. It was reported that half of the infants experienced delays in language or psychomotor development, three children had strabismus and two were

followed up at age four because of hyperkinetic conduct symptoms (Sandtorv, et al., 2009). However no details about the specific assessments were included in the publication and data for individual outcomes were not reported for the methadone and buprenorphine exposed infants separately.

In a Finnish study, Salo et al. (2009) compared the development of 21 children prenatally-exposed to non-maintenance buprenorphine (used for recreational purposes) and 13 non-exposed children. Fourteen of the buprenorphine-exposed children were in foster care, and seven were residing with their biological mother, although nearly all of these latter children had been placed in alternative care at least once. At three years of age, children prenatally exposed to buprenorphine achieved significantly poorer standardised scores on the Cognitive (maternal care: $M\pm SD$=8.14±0.38; foster care: $M\pm SD$=9.29±0.91) and Language Scales (maternal care: $M\pm SD$=18.00±2.00; foster care: $M\pm SD$=19.21±2.80) of the BSID-III, compared with the non-exposed children (Cognitive Scale: $M\pm SD$=10.54±1.26, F = 8.33, p < .01; Language Scale: $M\pm SD$=23.69±2.13, F = 9.91, p < .001). After adjusting for covariates (including birth weight and height, gestational age, maternal age, SES and number of foster placements), only the Language Scale scores remained associated with substance-exposure. The authors noted that the majority of buprenorphine-exposed children were also prenatally exposed to other substances along with illicit buprenorphine use (Salo, et al., 2009).

1.11 Temperament after prenatal exposure to opioids

Few studies have examined the construct of temperament in substance-exposed infants and children. However many researchers have used observations of behaviour and measures such as the Brazelton Neonatal Behavioural Assessment Scale (NBAS) to examine self-regulatory behaviour, such as responsiveness, activity, irritability, and consolability, in infants prenatally exposed to opioids (Chasnoff, et al., 1982; Chasnoff, et al., 1984; Jeremy & Bernstein, 1984; Jeremy & Hans, 1985; Lodge, et al., 1975; Ramer & Lodge, 1975; van Baar, Fleury, Soepatmi, et al.,

1989). The Brazelton NBAS appears to assess similar constructs to those examined in temperament testing (e.g. irritability, response to stimuli, activity levels and state lability) and scores on the NBAS of non-exposed infants have been shown to be correlated (r =.33 to .65) with analogous infant temperament scale scores, as rated by caregivers (Sostek & Anders, 1977).

In the first few weeks or months of life, infants exposed to opioids *in utero* are susceptible to high rates of neurobehavioural difficulties associated with Neonatal Abstinence Syndrome (NAS) (Finnegan, 1990). The constellation of symptoms displayed by infants with NAS has been likened to the 'difficult' temperament profile described by Thomas and Chess (Jeremy & Bernstein, 1984; 1977). Problems with self confidence, poor self discipline and inattention, as rated by parents and school teachers, have been reported more frequently for opioid exposed children than for non-exposed controls (Davis & Templer, 1988; Wilson, et al., 1979).

1.11.1 Temperament after prenatal exposure to methadone and/or heroin

Wilson et al. (1973) documented the development of infants prenatally exposed to heroin (*n*=30) from birth to between 3 and 34 months of age. Twenty-four infants showed signs of NAS in the first few days of life, and 82% continued to experience symptoms (including restlessness, irritability, and tremors) for up to six months. Fourteen infants (47%) attended follow-up appointments for 12 months or more and it was reported that seven of them continued to demonstrate 'behavioural disturbances', including poor attention span, hyperactivity, sleep problems, temper tantrums, and low frustration tolerance, as assessed by maternity and infant care clinic staff. The authors reported that the frequency of behavioural problems in this sample was high (50%) compared with a group of 'high-risk' non-exposed infants (6/271, 2%), however further details of the non-exposed sample were not published. The authors speculated that children residing in a chaotic home environment might display behavioural problems such as those observed in the study. However, as all of the heroin-exposed children with reported behavioural difficulties were residing with foster families at the time of assessment, influence of

home environment was thought not to be associated with child behavioural outcome (Wilson, et al., 1973). Limitations of this study were low rates of participant follow-up and lack of information regarding important covariates, such as length of time a child had been in foster care and measurement of the quality of the home environment.

A further study by this research group (Wilson, et al., 1979) reported that preschool aged children, prenatally exposed to heroin (n=22), were rated by their parents or caregivers as significantly more aggressive, impulsive, and as having more social difficulties than children considered to be (i) medically 'high-risk' (n=15), (ii) children raised in a 'drug environment' but with no prenatal exposure to any substance (n=20), and (iii) a group of children of similar socioeconomic background (n=20). Specifically, children prenatally exposed to heroin were reported to have significantly more parent-rated problems than their non-exposed peers in terms of temper control, aggression, impulsive behaviour, self-confidence and maintaining friendships, as measured on the Child Behaviour Rating Scales (Wilson, et al., 1979). However, as no mean scores or SDs were published, it is difficult to interpret these findings. The authors reported that the groups were comparable in terms of parental educational level, single parent status and home environment, and analyses were adjusted for children's age, gender, ethnicity, SES, and school readiness. The authors commented that the only difference between the groups was that a significantly greater proportion of the heroin-exposed children (50%) did not reside with their biological mother (Wilson, et al., 1979). However, the proportion of non-exposed children in alternative care was not provided.

This same group of researchers (Wilson, 1989; Wilson, et al., 1981) examined the development of a group of infants prenatally exposed to heroin (n=29) with that of infants prenatally exposed to methadone (n=39) and a non-exposed control group (n=57). Following discharge from hospital, caregivers rated the prevalence of excessive crying to be significantly greater for the methadone-exposed group of infants (49%) than for the non-exposed group of infants (15%, χ^2=10.8, p<.01).

Disturbances of sleep were reported significantly more frequently for infants prenatally exposed methadone (80%) compared with the non-exposed control group (50%, χ^2 =6.04, p<.05). While the prevalence of both problems was greatest for the heroin-exposed infants (excessive crying: 58%; sleep problems: 96%), prevalence did not differ significantly from the methadone-exposed group and statistical data were not presented for these comparisons. Parent-rated prevalence of hypertonia was significantly greater for infants born to untreated heroin users (52%) when compared with infants prenatally exposed to methadone (22%, χ^2 =4.54, p<.05). The prevalence of hypertonia was comparable for the methadone-exposed group and the non-exposed group of infants (20%) (Wilson, 1989; Wilson, et al., 1981).

Ramer and Lodge (1975) reported that of 34 infants prenatally exposed to methadone, 76% experienced withdrawal symptoms in the neonatal period (with 41% showing moderate to severe symptoms). Fifty nine percent of infants required pharmacological treatment for NAS, although length of treatment was not reported. Further, symptoms of irritability, excessive crying and tremulousness persisted up until six weeks of age for 38% of the infants (Ramer & Lodge, 1975). The authors reported that approximately 50% of the sample was also exposed to heroin *in utero*, however data were not provided separately for the two groups of infants. The majority of the infants (88%) were included in a longitudinal follow up study, described below (Lodge, et al., 1975).

Lodge and colleagues (1975) found that infants prenatally exposed to methadone and/or heroin (*n*=27) were significantly less alert than a group of non-exposed infants (*n*=10) (*M±SD*=3.84±1.70 vs. *M±SD*=5.40±1.84, t =2.40, p<.05) and had significantly poorer visual orientation and following response (*M±SD*=3.80±1.85 vs. *M±SD*=5.30±1.30, t =3.30, p<.01) when assessed on the Brazelton NBAS within the first week of life. Opioid-exposed infants also showed significantly increased levels of hypertonicity (*M±SD*=6.80±1.35 vs. *M±SD*=5.10±0.88, t =3.66, p<.001), activity (*M±SD*=5.80±1.35 vs. *M±SD*=4.80±1.23, t =2.02, p<.05), state lability (*M±SD*=5.32±1.31 vs.

M±SD=3.90±1.20, *t* =2.96, *p*<.01) and irritability (*M±SD*=5.54±2.02 vs. *M±SD*=3.80±1.14, *t* =2.55, *p*<.05) when compared with the non-exposed group (Lodge, et al., 1975). When the opioid-exposed subgroups were examined separately, infants prenatally exposed to heroin only (*n*=9) were rated more similarly to the non-exposed control group (*n*=10) on many of these items. The performance of infants prenatally exposed methadone only (*n*=12) was generally poorer, whereas infants prenatally exposed to a combination of heroin and methadone (*n*=6) performed the most poorly. That is, infants in the heroin/methadone subgroup had the lowest levels of alertness and visual orientation, and the highest levels of hypertonia, activity, state lability and irritability. This was particularly evident for activity levels, where infants prenatally exposed to heroin/ methadone had significantly greater activity levels (*M±SD*=7.00±0.00) than both the heroin-only sub group (*M±SD*=5.12±1.64, *t* =2.77, *p*<.05) and the non-exposed control group (*M±SD*=4.80±1.23, *t* =4.32, *p*<.001). Mean activity levels of the methadone-only sub group (*M±SD*=5.36±1.12) did not differ significantly from the other groups' mean scores (Lodge, et al., 1975). The authors reported that infants in the heroin/ methadone-subgroup experienced significantly greater severity of NAS symptoms (*M*=2.29, *p*<.01), as scored on a four point scale (0=no symptoms to 3=severe symptoms), and a greater proportion of this subgroup required pharmacological treatment for NAS (71%); compared to the methadone-only subgroup (NAS severity score: *M*=0.92; proportion requiring treatment: 54%) and the heroin-only subgroup (NAS severity score: *M*=1.22; proportion requiring treatment: 33%). While the authors cautioned that these results should be tentatively interpreted due to the small group numbers, it is also difficult to interpret the information about NAS severity, as no details about the scoring criteria were provided (Lodge, et al., 1975).

Research by Chasnoff et al. (1982; 1984) compared the development of infants prenatally exposed to methadone (*n*=39), to that of poly-drug exposed infants (i.e. combinations of benzodiazepines, marijuana and other illicit substances, *n*=19) and a non-exposed comparison group (*n*=27). When tested on the Brazelton NBAS at two days of age, infants prenatally exposed

to methadone performed significantly more poorly on tasks of orientation (e.g. visual inanimate orientation: $M \pm SD$=3.25±2.17) and motor maturity ($M \pm SD$=3.26±1.35) than the poly-drug exposed infants (visual inanimate orientation: $M \pm SD$=5.67±2.12; motor maturity: $M \pm SD$=4.50±1.43) and the non-exposed infants (visual inanimate orientation: $M \pm SD$=5.48±1.94, p<.001; motor maturity: $M \pm SD$=4.67±1.73, p<.01). This study also found that non-exposed infants scored significantly better on measures of state control (e.g. consolability: $M \pm SD$=6.50±1.56) than both the methadone-exposed infants ($M \pm SD$=4.52±2.42) and the poly-drug exposed group ($M \pm SD$=3.67±2.24, p<.001) (Chasnoff, et al., 1982; Chasnoff, et al., 1984).

Van Baar et al. (1989) found no significant differences in an early neonatal (40 weeks post-conception) Brazelton NBAS assessment between a group of infants prenatally exposed to combinations of methadone, heroin and cocaine (n=28) and a non-exposed control group of infants (n=37). Infants' performances were recorded as number of deviations from the optimum category (van Baar, Fleury, Soepatmi, et al., 1989). Scores for motor responses for the substance-exposed infants were poorer (median deviation: 2.33; range=0.33-3.83) compared with the non-exposed group (median deviation: 2.00; range=0.33-3.83). At a later assessment (44 weeks post-conception) motor performance of the substance-exposed group continued to be worse (median deviation: 2.17; range=0.67-3.17) compared with the non-exposed group (median deviation: 1.83; range=0.33-4.50, p=.10). Interactive responses were poorer for the methadone-exposed group (median deviation: 2.19; range=0.71-5.25 vs. median deviation: 2.13; range=0.25-4.75, p=.06), indicating that the substance-exposed infants were not as responsive to their environment as the non-exposed infants. Additionally, substance-exposed infants were more active than the non-exposed infants (median deviation: 3.20; range=1.60-5.00 vs. median deviation: 3.00; range=2.00-5.00), although this difference was not significant (van Baar, Fleury, Soepatmi, et al., 1989). When this group of infants was assessed at three months of age, substance-exposed infants were considered more active compared with the non-exposed infants (median: 3.67; range=2.20-4.75 vs. median: 3.32; range=1.75-5.25, p=.05). The authors suggested that this greater level of activity

could be related to sub-acute symptoms of NAS (van Baar, Fleury, & Ultee, 1989). At nine months of age, caregiver-rated temperament scores, including those pertaining to activity level, positive response, reactions to stimuli, and soothability, did not differ significantly between the two groups, although results suggested that the substance-exposed infants had a longer duration of orientation toward a single object (median: 4.00; range=2.00-5.64) when compared with the non-exposed infants (median: 3.44; range=2.18-5.27, p=.08) (van Baar, Fleury, & Ultee, 1989). A difficulty with interpreting these results is that scoring information was not provided for the temperament questionnaire used in the study.

Jeremy and Hans assessed 29 infants prenatally exposed to methadone on the Brazelton NBAS during the first week of life (approximately 2 days of age) and at one month of age, and compared the results to those of 37 non-exposed comparison infants (Jeremy & Hans, 1985). Groups were comparable in terms of maternal age, race, SES, education, prenatal care and parity, and infants were excluded if they were premature or small for gestational age (SGA). The authors reported that during the first week of life, after adjusting for possible confounding factors (birth weight, perinatal problems and delivery medication), infants prenatally exposed to methadone had significantly higher levels of irritability [M=5.00 vs.3.83, $F(1,60)$=5.54, p<.05], were significantly more active[M=4.62 vs. 3.86, $F(1,60)$=7.24, p<.01], more tremulous [M=7.35 vs.5.94, $F(1,60)$=10.76, p<.01], more hypertonic [M=6.79 vs.5.64, $F(1,60)$=13.81, p<.001], and had significantly lower levels of motor maturity [M=3.41 vs.5.28, $F(1,60)$=36.58, p<.001]. Additionally, methadone exposed infants were less cuddly, had higher levels of arousal, were more labile, less able to self sooth, and displayed more hand-sucking than the non-exposed infants. By one month of age the majority of these behaviours did not differ between the two groups, although the methadone-exposed group continued to have significantly increased muscle tone [M=6.59 vs.6.08, $F(1,61)$=3.89, p<.05] compared with the non-exposed infants. Methadone-exposed infants continued to show a tendency toward higher levels of arousal and poorer motor functioning when compared with the comparison group (Jeremy & Hans, 1985). The authors

suggest that the difficult behaviours displayed by the methadone-exposed infants in the first week of life, particularly those related to poor state control, irritability and responsiveness, may place them at risk of poor attachment relationships and poor interaction with caregivers (Jeremy & Hans, 1985). In another study by this group, the authors found that maternal-infant interaction was not predicted by maternal substance-use. Rather, maternal levels of psychological and psychosocial resources were associated with quality of interaction with infants. However, it was noted by the authors that the women in the methadone group generally had poorer levels of resources compared with the comparison group (Jeremy & Bernstein, 1984).

Davis and Templer (1988) compared the behaviour of children who were exposed to opioids (heroin and/or methadone, *n*=28) in pregnancy, with a group of reference children (*n*=28) who were not prenatally exposed to opioids but who resided with a father figure with an opioid-addiction. As described above, children were aged between six and 15 years at assessment. It was reported that children exposed to opioids in pregnancy had significantly more behaviour problems on most subscales of the Burks Behavioral Rating Scales, as rated by their school teachers, than non-exposed children. The exception to this was the Resistance subscale, although opioid-exposed children still scored more poorly than the non-exposed group. When the opioid-exposed group were examined independently, children exposed to methadone (n=12) were rated by teachers as having significantly more problems than heroin-exposed children (n=9) in terms of impulsiveness (*M±SD*=16.75±6.27 vs. *M±SD*=9.22±5.14, *t* =2.93, *p*<.01), anger control (*M±SD*=13.42±4.23 vs. *M±SD*=8.44±2.13, *t* =3.22, *p*<.01) and participating with peers in physical interactions (*M±SD*=10.33±3.42 vs. *M±SD*=7.44±1.94, *t* =2.27, *p*<.05). They were also rated as being significantly more withdrawn (*M±SD*=18.83±6.06 vs. *M±SD*=11.22±7.16, *t* =2.64, *p*<.05) than the heroin-exposed children. The authors suggested that the constellation of deficits displayed by the children exposed to opioids in pregnancy were consistent with the symptoms of attention deficit type disorders, including impulsive, under socialised and inattentive behaviours. Further, they indicated that the findings of poorer neurobehavioural functioning displayed by the

methadone-exposed children, compared to the heroin-exposed children, correlate with other

research showing that methadone-exposed infants experience greater severity of NAS symptoms

(Davis & Templer, 1988).

Weiss, Jonn-Seed, and Harris-Muchell (2007) found that six month old infants prenatally exposed

to cocaine or opiates (n=30) were rated more negatively, by their mothers, on all dimensions of

the Revised Infant Temperament Questionnaire, than infants not exposed to any substance in

pregnancy (n=90). Although the study found that infants prenatally exposed to substances were

significantly more distractible ($M\pm SD$ = 4.24±0.60 vs. $M\pm SD$ = 3.87±0.67, t(118)=2.55, p=.01) and

more intense in their expression of emotions ($M\pm SD$=4.36±0.86 vs. $M\pm SD$=4.00±0.65, t(118)=2.55,

p<.05) than their non-exposed peers, after adjusting for infant factors (i.e. gender, gestational

age, neonatal morbidity and ethnicity) and maternal factors (i.e. stress, quality of caregiving, child

maltreatment and perceived adequacy of income), only distractibility remained significantly

associated with substance exposure and accounted for 12% of the variance in distractibility

(p<.001). The authors suggested that the higher levels of distractibility observed in infants and

children prenatally exposed to substances may be associated with poor regulation of the arousal

and excitatory response (Weiss, et al., 2007). This supposition is supported by neurobiological

research which indicates that the area of the brain involved in the regulation of attention and

inhibitory control is the striatum (Herrero, Barcia, & Navarro, 2002; Roberts et al., 2004). It is

known that prenatal exposure to opioids can disrupt the normal development of the striatal

system, including alteration of opioid peptide levels and reduction in striatal nerve growth factor

content (Tempel, Yang, & Basheer, 1995; Tiong & Olley, 1988; Wu, et al., 2001), which may

account for high rates of distractibility and poor inhibition in opioid-exposed infants and children.

A limitation of this research is that all substance-exposed infants were prenatally exposed to more

than one substance (e.g. opioids, cocaine, marijuana, amphetamines) and analyses were not

conducted to investigate the separate effect of each substance on infant temperament. However

the authors noted that problems with distractibility and attention are not limited to prenatal

exposure to one specific substance, but have been found to correlate with prenatal exposure to alcohol, opioids, marijuana or cocaine (Weiss, et al., 2007).

1.11.2 Temperament after prenatal exposure to buprenorphine

Only one study has described the self-regulatory behaviour of infants prenatally exposed to buprenorphine. This study, which examined three month old infants in Norway, found no differences in sleep patterns, amount of day or night time wakefulness, or the number of episodes of day-time distress, between 35 infants prenatally exposed to opioid maintenance medication (methadone n=24, buprenorphine n=11) and a group of 36 comparison infants (Sarfi, Martinsen, Bakstad, Røislien, & Waal, 2009). The authors found that infants prenatally exposed to methadone or buprenorphine had fewer parent-rated episodes of night-time distress ($M\pm SD$=1.4±1.2) than non-exposed infants ($M\pm SD$=2.0±1.5), although this difference did not reach statistical significance (p=.07). These similarities in self-regulation were evident despite worse neonatal outcomes for the infants prenatally exposed to maintenance medication. These were significantly lower birth weight ($M\pm SD$=3148±608 gm vs. $M\pm SD$=3618±343 gm, p<.001), lower gestational age ($M\pm SD$=38.7±2.5 weeks vs. $M\pm SD$=39.5±0.9 weeks, p<.08), and a high rate of NAS (60%). Values were not provided separately for infants prenatally exposed to buprenorphine or methadone, thus it is difficult to draw strong conclusions about buprenorphine-exposure from this research. The authors noted that intensive pre- and post-natal support (including the provision of adequate housing or residential parenting assistance services) is available in Norway for women in maintenance treatment programs, and was utilised by women in their study. They suggested that this psychosocial support, along with the lack of other illicit drug use may have contributed to the positive outcomes observed for the opioid-exposed infants (Sarfi, et al., 2009).

1.12 The contribution of maternal and environmental factors to child developmental outcome

Problems with behaviour, temperament and developmental delay in infants prenatally-exposed to narcotics are very often attributed to substance-exposure; however it is important to examine

the contribution of other influences on a child's development (Bernstein & Hans, 1994; Black, Schuler, & Nair, 1993).

Research with non-drug using populations has shown that maternal depression and poverty is associated with poorer developmental outcomes in both infants and children (Beckwith, Howard, Espinosa, & Tyler, 1999; Grace, Evindar, & Stewart, 2003; Petterson & Albers, 2001; Whiffen & Gotlib, 1989). Infants of women experiencing postpartum depression perform less well on cognitive measures and exhibit fewer positive emotions than infants of non-depressed mothers. Depressed women are also more likely to perceive their infants as more bothersome and more difficult to care for, and are less likely to engage with them in active, playful and responsive interactions than are non-depressed women (Whiffen & Gotlib, 1989). Postpartum depression may continue to have an effect on a child's cognitive performance and behavioural disturbance, particularly in boys, until school age, even when maternal symptoms have remitted (Beckwith, et al., 1999; Grace, et al., 2003).

Ongoing maternal depression has also been studied in relation to infant mental health and early childhood development (Seifer, Dickstein, Sameroff, Magee, & Hayden, 2001). Correlations between kindergarten-aged children's social and emotional competence have been found with maternal depression scores; while increased incidence of teacher- and parent-rated behaviour problems have been associated with exposure to maternal depression (Essex, Klein, Miech, & Smider, 2001). A study of over 7,500 mother-child dyads found that maternal depression was associated with poorer cognitive and motor development in two to four year olds. Additionally, chronic maternal depression had a greater detrimental effect on children's development than transitory maternal depression (Petterson & Albers, 2001).This study also found that poverty (defined as living below the U.S. Census poverty line) was negatively associated with toddlers' performance on cognitive items of the Denver Developmental Screening Test (DDST) (Petterson & Albers, 2001). Poverty was inversely related to children's motor performance, with toddlers from

poorer families significantly more likely to be toilet trained, and to be able to perform every-day motor tasks such as dressing themselves, and pedalling a tricycle, than children from higher income households.

A study examining the relationship between birth weight and cognitive functioning among children in Port Pirie, South Australia, followed children through early and middle childhood (Tong, Baghurst, & McMichael, 2006). Children's cognitive functioning at two years of age was significantly related to birth weight; however the magnitude of the association between cognitive functioning and birth weight attenuated over time and became non-significant later in childhood. The authors found that at the later assessments, socio-environmental factors, including socioeconomic status, maternal IQ, quality of the home environment and children's lead exposure, substantially contributed to children's cognitive functioning (Tong, et al., 2006).

There is increasing interest in examining the developmental outcome of children exposed to multiple environmental risk factors, including maternal depression, poverty, domestic violence, single parent families, home environment, and parenting stress. Each of these variables has been found to exert an influence over child outcomes including cognitive functioning, social development, health and growth (Petterson & Albers, 2001; Ram & Hou, 2003; Thernlund & Samuelsson, 1993). A study exploring the effect of cumulative risks on children's intellectual functioning identified a set of risk variables that predicted verbal IQ scores and social-emotional outcome at four years of age. These ten risk factors were: maternal mental health, maternal anxiety, maternal attitude toward parenting, maternal-child interaction, maternal education, parental occupation, minority status, maternal social support, stressful life events, and family size. The authors established that no single risk factor contributed exclusively to intellectual functioning, however as the number of risks increased, children's intellectual performance declined (Sameroff, Seifer, Barocas, Zax, & Greenspan, 1987).

Relationships between maternal mental-health, mother-infant attachment, child temperament, home environment, and other risk factors have been shown to play an important role in determining the developmental outcome of substance-exposed infants and children (Bernstein & Hans, 1994; Black, et al., 1993; Jeremy & Bernstein, 1984). Bernstein and Hans (1994) noted that while research has found differences in development between drug-exposed children and non-exposed controls, effect sizes have generally been small. Further, the authors noted that prenatal drug exposure is rarely the sole element of developmental risk experienced by children of drug users (Bernstein & Hans, 1994).

The prevalence of psychopathology, including depression, anxiety and antisocial behaviours, in persons taking illicit drugs is very high. For example, the prevalence of depressive disorders amongst populations seeking treatment for opioid dependence has been reported to range from 35% to over 50% (Beckwith, et al., 1999; Hans, Bernstein, & Henson, 1999; Kessler et al., 1996; Kosten, Morgan, & Kosten, 1990). Female substance abusers have been reported to be at greater risk of experiencing clinically significant levels of anxiety and depression than their male counterparts (Chander & McCaul, 2003; Hans, et al., 1999; Teesson et al., 2005). These findings, together with strong evidence that depression in non drug-abusing women has a negative effect on a number of areas of child development, increases the importance of examining the developmental outcome of children born to women who use illicit drugs during pregnancy (Beckwith, et al., 1999; Essex, et al., 2001; Hipwell, Goossens, Melhuish, & Kumar, 2000; Murray, Fiori-Cowley, Hooper, & Cooper, 1996; Patel, DeSouza, & Rodrigues, 2003; Seifer, et al., 2001).

Difficulties with mother-infant bonding have been observed for opioid-using women even prior to delivery. Mikhail and colleagues found that methadone-maintained pregnant women had significantly lower maternal-foetal attachment scores than women with no drug abuse history (Mikhail, Youchah, DeVore, Ho, & Anyaegbunam, 1995). One of the earlier studies evaluating parenting and depression in methadone maintained mothers found strong negative correlations

between higher depression scores and attendance for antenatal care (Finnegan, Oehlberg, Regan, & Rudrauff, 1981). This study concluded that that whilst drug-dependence is not necessarily an indicator of inadequate parenting skills, the environment in which many drug-exposed children are raised may contribute to increased risk of child abuse and neglect (Finnegan, et al., 1981). A study by Hans, Bernstein and Henson (1999) found that opioid-dependent mothers were more likely than non-dependent mothers to meet criteria for a variety of mental health problems, and that poorer mental health was related to difficult interactions with infants, including insensitive, harsh and unresponsive parenting in this population (Hans, et al., 1999). Problems with poor attachment and depression in substance using mothers may thus have dire implications for their infants' already poorer expected outcomes.

Black, Schuler and Nair (1993) studied the relationships between the home environment, parenting stress and neurological performance on the Brazelton NBAS amongst 20 infants prenatally exposed to cocaine and other substances, including heroin and marijuana, and a control group of non-exposed infants (n=20). They found that at six weeks of age, infants exposed to substances *in utero* showed greater autonomic instability than non-exposed infants (Black, et al., 1993). No significant group differences were evident in terms of parental nurturance, child-centred home environment or parenting stress, however there was a trend for mothers in the control group to provide a more child-centred and nurturing care-giving environment than the mothers in the substance-using group. The authors also found that infants who were raised in a child-centred environment (regardless of drug-exposure status) performed better on infant neurodevelopmental assessments, were less depressed, and demonstrated lower levels of excitability (Black, et al., 1993).

A more recent study by this research group examined the relationship between cumulative environmental and psychosocial risk factors, parenting attitudes and child development in a group of substance-using women and their infants (n=161) (Nair, Schuler, Black, Kettinger, & Harrington,

2003). Over 70% of participating women reported depressive symptoms and negative life events, including incarceration, homelessness and domestic violence. Results indicated that as the number of risks increased, women reported greater levels of parenting stress and child abuse potential. However, no relationship was found between levels of risk and children's development on the BSID at six or 18 months of age (Nair, et al., 2003). The authors suggested that there may have been no relationship between cumulative risk and infant development in their study due to the age of the children. They postulated that psychosocial risk factors may exert greater influence on development in preschool and school aged children (Nair, et al., 2003).

A study by Carta and colleagues (2001) examined the effects of prenatal substance exposure and environmental risk on children's developmental trajectories from three to 57 months of age, in a sample of substance exposed (n=137) and non-exposed children (n=141). The authors found that individually, prenatal substance exposure and environmental risk negatively influenced children's development. Further, children with higher levels of risk developed more slowly over time than children with lower risk levels, and that the gap between the two groups widened as the children aged. When substance exposure and environmental risk were entered into the same statistical model, only environmental risk remained significantly related to developmental outcome (Carta, et al., 2001).

Modest correlations (r=.28=.38) have been observed between home environment scores on the Home Screening Questionnaire (HSQ) and mean IQ scores on the WPPSI-R, WISC-III and Stanford-Binet Intelligence Scale (Azuma & Chasnoff, 1993; Chasnoff et al., 1998). Chasnoff and colleagues examined the cognitive development of children prenatally exposed to cocaine (n=95) and a non-exposed comparison group (n=75) between the ages of four and six years (Chasnoff, et al., 1998). This study found that lower HSQ scores, indicating poorer home environment, were strongly correlated with increased levels of maternal substance use. Although IQ scores on the WPPSI-R and WISC-III did not differ significantly between the two groups of children in univariable

analyses, in path analyses there was an indirect effect of prenatal substance-exposure on IQ scores that was mediated by the quality of the home environment. That is, children prenatally exposed to substances experienced a poor quality home environment, which was subsequently related to lower performance on tests of cognitive development. However, this study also found that quality of the home environment was not associated with behavioural problems, as assessed on the Child Behaviour Checklist (CBCL). Rather prenatal substance exposure was associated with worse behavioural outcomes. The exception to this was child self-regulation (encompassing children's' scores on the Aggressive Behaviour, Delinquent Behaviour, Attention Problems and Social Problems scales), in which better home environment was associated with better capacity for self-control, regardless of group status (Chasnoff, et al., 1998).

As described above, Wilson (1989) found that children's cognitive performance fluctuated over time, when assessed on the MDI of the BSID at 9, 18 and 24 months of age, and on the McCarthy Scales between the ages of three and five years. She reported that uneven performances were most obvious amongst the heroin-exposed children compared with those exposed to methadone or a non-exposed group. Additionally, fluctuations in developmental performance occurred most frequently in children who resided in an unstable or disadvantaged home environment. It was suggested by the author that environmental changes may have a considerable effect on a child's cognitive functioning, and for this reason it was posited that longitudinal, rather than cross-sectional studies, were more useful in examining the development of this population of children (Wilson, 1989). This view is supported by other research which has indicated that the relationship between early scores on the HOME scale (i.e. those obtained at ≤ 12 months of age) are generally only moderately correlated with tests of cognitive development; and that the association between HOME scores and cognitive development appears to gain strength over the second year of life (Bradley, 1994; Totsika & Sylva, 2004).

In a study examining the influence of environmental risks on children's development, Ornoy and colleagues (2001) compared the development of children with prenatal exposure to heroin raised by their biological mothers (*n*=31), with that of children who were not prenatally exposed to heroin, but who resided with a father who was heroin-dependent (*n*=33), a group of children prenatally exposed to heroin but living in foster homes (*n*=34), and two groups of non-exposed children who were from low SES (*n*=32) and average SES (*n*=30) homes. This study found that when assessed at an average age of eight years, children residing with substance-dependent parents, and those in the low SES group, had significantly poorer home-environments, assessed on the Caldwell HOME scale, than both the average SES group and the heroin-exposed children who were residing in foster homes. This study also found that while mean Verbal and Performance IQ scores on the WISC-R of all children were within the average range, children prenatally exposed to heroin and living with a heroin using mother achieved significantly lower mean scores (Verbal: *M*±*SD*=102.0±8.8; Performance: *M*±*SD*=101.0±24.0) than children prenatally exposed to heroin but living in foster homes (Verbal: *M*±*SD*=108.3±17.6; Performance: *M*±*SD*=106.2±24.9, *p*<.05). Scores of children residing in low SES households were also significantly lower than those of the adopted children (Ornoy, et al., 2001). This study did not examine the respective contributions of substance-exposure and home environment to child development scores, neither were correlations between the WISC-R and HOME scores discussed.

1.13 Thesis rationale and study aims

Prenatal exposure to illicit substances increases the risk of poorer pregnancy outcomes, growth deficits, neurodevelopmental problems and behavioural difficulties in exposed infants and children, compared with their non-exposed peers (Adams, et al., 1989; Berlin, et al., 1998; Chang, et al., 1992; Kandall, et al., 1976; Laken, et al., 1997; Robins & Mills, 1993). In many countries, including Australia, pharmaceutical maintenance with methadone is the first line treatment for pregnant opioid-dependent women (Dunlop, et al., 2003; Lintzeris, et al., 2006). Benefits for women maintained on methadone during pregnancy include reduction in obstetric complications,

stabilisation of plasma drug concentrations, and engagement in a more stable lifestyle. Infants prenatally exposed to methadone are less likely to be small for gestational age (SGA), have low birth weight, or have problems related to feeding, settling and hypertonicity, than infants prenatally exposed to illicit opioids (Australian Drug Foundation, 2005b; Chang, et al., 1992; Dunlop, et al., 2003; Lintzeris, et al., 2006; Lejeune, 2006 #111). Whilst treatment with methadone during pregnancy results in fewer complications for both mother and infant when compared with the use of illicit opioids, its use in pregnancy is associated with high rates of neonatal abstinence syndrome (NAS), and has been independently associated with long term developmental and behavioural deficits for exposed infants and children (Bernstein, Jeremy, Hans, & Marcus, 1984; Davis & Templer, 1988; Finnegan & Kandall, 1997; R. E. Johnson, Jones, et al., 2003; Marcus, Hans, & Jeremy, 1984; van Baar, Fleury, Soepatmi, et al., 1989; van Baar, et al., 1994). In particular, smaller growth percentiles (Hans, 1989; Hunt, et al., 2008; Lifschitz, et al., 1983, 1985; Soepatmi, 1994), delayed or absent responses to VEP (Hamilton, et al., 2010), and poorer cognitive and motor development outcomes (Davis & Templer, 1988; Hunt, et al., 2008; H. L. Johnson, et al., 1987, 1990; H. L. Johnson & Rosen, 1982; Rosen & Johnson, 1982; van Baar & de Graaff, 1994).

Buprenorphine hydrochloride is now widely used in the treatment of non-pregnant opioid-dependent individuals, and there is a growing body of research to support its safety and efficacy during pregnancy and the early neonatal period (Gordon, 2006; R. E. Johnson, Jones, et al., 2003; Jones, et al., 2005; Jones, et al., 2010; Kayemba-Kay's & Laclyde, 2003; Lacroix et al., 2004; Lejeune, et al., 2006). However, buprenorphine has not yet been recommended for use during pregnancy, because its safety, efficacy and effectiveness have not yet been firmly established for pregnant women and their infants (Lintzeris, et al., 2006). Further, information regarding longer term developmental outcomes for children prenatally exposed to buprenorphine is scarce. Studies describing the development beyond the neonatal period, for infants prenatally exposed to buprenorphine, have had very small sample sizes (N = 2 to 13), and the majority have not included

a comparison to methadone exposure (Kahila, Kivitie-Kallio, et al., 2007; Kayemba-Kay's & Laclyde, 2003; Schindler, et al., 2003). Two Norwegian studies have described longer term outcomes for infants prenatally exposed to methadone or buprenorphine (Sandtorv, et al., 2009; Sarfi, et al., 2009). The first study compared sleep–wakefulness–distress patterns of three month old infants prenatally exposed to methadone or buprenorphine (n=35) with those of a group of non-exposed comparison infants (n=36) (Sarfi, et al., 2009). The other study provided an overview of the development of infants prenatally exposed to methadone or buprenorphine (n = 15) to an average of 30 months of age. However, no details about the measures were included in the second publication, and neither study reported results separately for the buprenorphine and methadone exposed infants.

While methadone maintenance appears to be effective and widely acceptable in the treatment of opioid-dependence in pregnancy, there are some concerns regarding the long term outcomes for prenatally exposed children. Additionally, negative associations with methadone maintenance may discourage some women from seeking treatment for opioid addiction (Anstice, et al., 2009; Mattick, et al., 2003; Murphy & Irwin, 1992). Therefore, research into alternative pharmacotherapies that are safe and effective in pregnant populations is needed (Davids & Gastpar, 2004; Lintzeris, et al., 2006; Mattick, et al., 2003). Use of buprenorphine for treatment of opioid-dependence has increased due to its partial agonist properties, which produce milder withdrawal effects and may be safer in overdose. In addition, its extended duration of action can allow for longer periods between doses. Further, it appears that buprenorphine is comparable to methadone in terms of safety and efficacy in pregnancy, and may result in a reduction in the duration and severity of NAS in exposed infants. Benefits of buprenorphine maintenance during pregnancy may also extend to reduced hospital stays for exposed neonates. This may reduce the health costs of caring for these infants (Jones, et al., 2010).

Much of the research on the developmental outcome of substance-exposed infants has targeted direct drug effects. As substance use seldom occurs in isolation from other bio-psychosocial problems, maternal substance use is unlikely to be the only risk factor for a child prenatally exposed to opioids. Risk factors such as poverty, poor household environment, low parental academic achievement, parental unemployment and parental mental illness may all contribute to poorer child developmental outcome. While some studies have examined the contribution of environmental risk factors to the development of substance-exposed children, many have not and it is therefore difficult to draw firm conclusions about the developmental effect of prenatal substance exposure (Carta, et al., 2001; Jones, Kaltenbach, & O'Grady, 2009; Nair, et al., 2003).

To date, no studies have comprehensively described the longer term outcomes of infants prenatally exposed to buprenorphine. The aim of the research described in this thesis was to compare the physical growth, neurological development, and temperament of infants prenatally exposed to buprenorphine, methadone, and a non-exposed control group. An additional aim was to explore the relationships between potential covariates and the developmental outcomes of children exposed to opioid maintenance medications in pregnancy. Overall, it was expected that the developmental outcomes of infants prenatally exposed to buprenorphine would not differ substantially from those of non-exposed infants. Additionally, it was anticipated that infants prenatally exposed to methadone would do more poorly on the measures examined, than both infants prenatally exposed to buprenorphine and a non-exposed control group of infants. Finally, it was expected that these differences in developmental outcome would remain stable over time. These expectations were applied to all outcome variables. Accordingly the following individual hypotheses were proposed:

Physical Growth

Hypothesis 1: The weight, length and HC of infants prenatally exposed to buprenorphine will not differ significantly from those of a non-exposed control group when assessed at four, 12 and 24 months of age.

Hypothesis 2: The weight, length and HC of infants prenatally exposed to methadone will be significantly smaller than those of infants prenatally exposed to buprenorphine and a non-exposed control group of infants when assessed at four, 12 and 24 months of age.

Hypothesis 3: Change in weight, length and HC over time will not vary significantly between children prenatally exposed to buprenorphine, methadone, or in a non-exposed control group.

Neurological Development

a) Visual Evoked Potentials

Hypothesis 4: P1 latencies of infants prenatally exposed to buprenorphine will not differ significantly from those of a non-exposed control group, when measured at four months of age.

Hypothesis 5: Infants prenatally exposed to buprenorphine will have significantly shorter P1 latencies at four months of age, suggesting greater visual maturation, than children prenatally exposed to methadone.

b) Bayley Scales of Infant Development

Hypothesis 6: The mental, motor and behavioural scores of infants prenatally exposed to buprenorphine will not differ significantly from a non-exposed control group when assessed at 12 and 24 months of age.

Hypothesis 7: The mental, motor and behavioural scores of infants prenatally exposed to methadone will be significantly lower than those of infants prenatally exposed to buprenorphine and a non-exposed control group of infants when assessed at 12 and 24 months of age.

Hypothesis 8: Change in mental, motor and behavioural scores over time will not vary significantly between children prenatally exposed to buprenorphine, methadone, or in a non-exposed control

<u>*Temperament*</u>

Hypothesis 9: Temperament scores of infants prenatally exposed to buprenorphine will not differ significantly from a non-exposed control group when assessed at four, 12 and 24 months of age.

Hypothesis 10: The temperament scores of infants prenatally exposed to methadone will be significantly lower, indicating easier temperament, than those of infants prenatally exposed to buprenorphine and a non-exposed control group of infants when assessed at four, 12 and 24 months of age.

Hypothesis 11: Change in temperament scores over time will not vary significantly between children prenatally exposed to buprenorphine, methadone, or in a non-exposed control group.

CHAPTER 2

Study Design and Methodology

The first section of this chapter describes the overall design of the research study, the recruitment of participants, ethics approval, consent processes, and the response and retention of participants. The second section describes the assessment and statistical methods employed.

2.1 Study Overview

The study which forms the basis of this thesis is the second phase of a prospective longitudinal research project. The overarching longitudinal research project was designed to examine the safety and efficacy of the opioid maintenance drug buprenorphine, during pregnancy, the neonatal period, and early childhood. Research presented in this thesis comprises the early childhood period.

To distinguish the research presented in this thesis from the first phase in the longitudinal research project, the first phase will be referred to as 'the pregnancy and neonatal phase', while the second phase (the research presented in this thesis) will be referred to as 'the early childhood phase'.

The pregnancy and neonatal phase of the prospective longitudinal research project commenced in early 2002. During this phase, pregnant women who were opioid-dependent were enrolled in an open-label, non-randomised, flexible-dosing trial examining the safety and efficacy of buprenorphine, compared with methadone, throughout pregnancy and the neonatal period. Pregnant, non opioid-dependent women were recruited as controls. At each ante-natal visit and weekly after delivery, until their infant was four weeks old, women were assessed on measures of physical symptoms related to pregnancy, opioid withdrawal, and recent use of both licit and illicit

substances. Women with opioid dependence were also asked about side effects relating to their maintenance medication. Random urine samples were collected from all women (including controls) during the antenatal period to screen for illicit drug use. All infants born into the study were observed for signs of neonatal abstinence syndrome (NAS, opioid withdrawal) until discharge from hospital and then weekly until four weeks of age. Details about the results from the pregnancy and neonatal phase of the project are reported elsewhere (Gordon, 2006).

The early childhood phase of the longitudinal research project commenced in April 2003 and is the focus of this thesis. The aim of this phase was to examine prospectively the effects of prenatal exposure to maternal maintenance with buprenorphine or methadone on the neurological, psychological and physical development of the children at four, 12 and 24 months post-partum. The 87 families who completed at least one of these follow-up assessments between April 2003 and May 2009 are the focus of this thesis. At each follow-up assessment, mothers (or children's primary caregiver) completed a questionnaire assessing child health, feeding and sleeping, child temperament, child's care-giving environment, parent's mental health, parent-child interaction, parental social support, recent caregiver substance use and demographic characteristics. Neurological development was assessed using Visual Evoked Potentials (VEP) at four months of age, and the Bayley Scales of Infant Development, Second Edition (BSID-II) (Bayley, 1993) at 12 and 24 months. Physical development was monitored in terms of weight, length and head circumference (HC) at each assessment. A detailed description of the data collected is provided later in this chapter.

2.2 Recruitment

The following section describes the recruitment procedures for the longitudinal research project. Recruitment was initially undertaken during the pregnancy and neonatal phase of the study; however as a greater number of participants was required for the early childhood phase, I completed the recruitment of participants. While results from the pregnancy and neonatal phase

are not reported in this thesis [see (Gordon, 2006)], recruitment of participants is described as it is pertinent to the early childhood phase of the study.

Pregnant women with opioid dependence were recruited from outpatient clinics at two Drug and Alcohol Services South Australia (DASSA) drug treatment centres, a specialist drug and alcohol antenatal clinic at the Women's and Children's Hospital (WCH), and the high-risk pregnancy clinic at Flinders Medical Centre (FMC), in Adelaide, South Australia. Potential participants with opioid dependence were provided with information about the study by DASSA medical staff at each clinic when they first attended for an appointment. A research assistant then described the study in more detail, and administered the screening questionnaire (Appendix A).

Women were eligible to participate if at enrolment they were ≤28 weeks gestation, and were aged between 16 and 40 years. Women were excluded from the study if they were taking any medication that interacted with the maintenance drugs or was known to affect pregnancy outcome (e.g., medications for HIV, epilepsy, schizophrenia or other major psychiatric illness), had a self-reported level of alcohol use greater than seven standard drinks per week [i.e., higher than levels recommended by 2001 NHMRC guidelines for alcohol use in pregnancy (National Health and Medical Research Council, 2001)], were pregnant with more than one foetus, or were participating in another clinical research project that interfered with the present study.

Eligible women were provided with an information sheet (Appendix B), and consent was obtained either at that time or at the woman's next antenatal appointment (Appendix C). Separate consent for the enrolment of the woman's infant was also obtained (Appendix D). Women with opioid dependence were self-assigned to either buprenorphine-maintenance (BM) or methadone-maintenance (MM) treatment. It was not possible to randomly assign women to a treatment group for the purposes of the study because firstly, at the time of the longitudinal research project's implementation, research on the effects of prenatal exposure to buprenorphine was

only just beginning to emerge. While results generally appeared to be encouraging and there had been no reports of teratogenic effects (R. E. Johnson, Jones, et al., 2003), longer term effects of buprenorphine exposure were undocumented, and random assignation to BM or MM was considered unethical. Secondly, the prevalence of opioid-dependent pregnancies in the Adelaide metropolitan area was not sufficient to support an adequately powered randomised controlled trial without a protracted period of recruitment. In the majority of cases (74%), women in the two maintenance groups were already participating in a prescribed opioid program when they became pregnant. A small number of opioid-dependent women who were not enrolled in a maintenance program had requested treatment with BM or MM after discovering that they were pregnant.

Hospital records of non opioid-dependent women attending antenatal clinics at the WCH were examined to identify potential control subjects. This group of participants was included in order to provide an opioid-free comparison to the opioid-dependent pregnancies. A research assistant approached potential control participants in the waiting area of the clinics either immediately before or after their antenatal appointment to provide information about the study. As with the two maintenance group participants, women in the control group were screened to make sure they met the eligibility criteria (as described above), provided with an information sheet (Appendix E), and signed consent for themselves (Appendix F) and their infants' participation in the study (Appendix D). Women in the control group self-reported not using illicit opioids.

Demographic and lifestyle variables were collected from each participant during a face-to-face interview at enrolment (Appendix G). Due to the restricted sample pool, strict matching criteria were not applied; however groups were similar on a number of measures known to have an effect on pregnancy outcomes. These were maternal age, gravida (first pregnancy versus second or more), parity (first born infant versus second or more), self-reported alcohol use within the past month (Yes/No) and self-reported tobacco use within the past month (Yes/No) (see Table 3.1).

2.3 Ethical Approval

Ethics approval for the pregnancy and neonatal phase of the study was obtained from the University of Adelaide, Flinders Medical Centre Research Ethics and Clinical Drug Trials committees (Protocol number 130/045) and the Women's and Children's Hospital Human Research Ethics Committee (Project number REC1330/6/2005). The early childhood phase of the study was approved by the University of Adelaide Committee on the Ethics of Human Experimentation Psychology Department subcommittee, the Women's and Children's Hospital Human Research Ethics Committee (Project number REC1348/7/2005), and the Flinders Clinical Research Ethics and Clinical Drug Trials Committees, Flinders Medical Centre (Protocol number 130/045).

Participants received three payments of $A50 during the pregnancy and neonatal phase of the study as compensation for their time and any inconvenience experienced due to their participation. They were also provided with a payment of $A50 and a small age-appropriate gift for their child at each of the three follow-up assessments in the early childhood phase of the study. Payment of study participants has been viewed by some as coercive or inappropriate, particularly when the sample involves a marginalised population, such as economically disadvantaged individuals or those with substance dependence (Dickert & Grady, 1999; Festinger et al., 2005; Sears, 2001). Recent research examining the views of adults with substance dependence in the United States has indicated that monetary reimbursement for study participation was seen by participants as necessary and appropriate for attracting potential study recruits. Reimbursement for participation in research was viewed as an honest source of income and participants rejected the idea that payment would increase their risk of relapse (Slomka, McCurdy, Ratliff, Timpson, & Williams, 2007). Other research has found that monetary incentives to participate in research studies were not linked to increases in substance use or perceptions of coercion among participants (Dempsey, Back, Waldrop, Jenkins, & Brady, 2008; Festinger, et al., 2005; Festinger, Marlowe, Dugosh, Croft, & Arabia, 2008). Further to this, larger payment

amounts (i.e. ≥US$40 vs. $10 or ≥US$100 vs. $70) have been shown to increase the likelihood of attendance at follow-up appointments, thus reducing researcher time and costs related to tracing participants (Festinger, et al., 2005; Festinger, et al., 2008). Festinger et al. (2005; 2008) also found that participants who received cash payments were more likely to spend the money on everyday essential items such as household expenses compared with those who received gift certificates. We therefore considered that a mid-range cash payment of $A50 and a small age-appropriate toy or book for the child was reasonable reimbursement for participation in a study which required a long term commitment.

2.4 Participants

Response and retention for each phase of the study

The study design and flow of participants through each stage of the study is summarised in Figure 2.1.

The Pregnancy and Neonatal Phase

One hundred and forty eight women were approached to participate in the longitudinal research project. Nineteen women (group unknown) were either unwilling to participate (*n*=9, reasons unknown) or did not meet inclusion criteria (n=10). One woman was enrolled into the BM group at 31 weeks gestation as she wished to remain on buprenorphine maintenance throughout the remainder of her pregnancy and one woman was enrolled into the BM group the day following delivery because she had not attended any of her ante-natal visits at the delivery hospital. Because these women were maintained on buprenorphine during their pregnancies, hospital policy required that the infants were monitored for Neonatal Abstinence Syndrome (NAS) and both women agreed to enrolment in the follow-up study. One woman was initially enrolled into the BM group at 16 weeks gestational age. This woman subsequently requested a change in maintenance treatment before her next antenatal appointment (at 21 weeks gestation), and her data were therefore included in the MM group. Two women in the MM group agreed to

participate in the study prior to 28 weeks gestation but data were not collected from them until later gestational ages. One control participant was enrolled one month prior to turning 16 years of age. Thus 129 women (87% of 148 women approached) were enrolled in the longitudinal research project (52 BM, 39 MM and 38 controls). In an effort to minimise participant attrition, and to provide a link between the two phases of the study, I organised to meet participants during at least one antenatal appointment during the pregnancy and neonatal phase of the study. Twenty three women were not eligible for inclusion in the subsequent early childhood phase of the study on which this thesis is based. Reasons for discontinuation varied between groups. Details are presented for each group separately below.

Nine women and four infants in the BM group were not able to be included in the early childhood phase of the study: three women were withdrawn after miscarriage (considered by their obstetrician to be unrelated to buprenorphine) prior to 20 weeks gestation, two women were withdrawn after seeking termination of pregnancy, two women withdrew one week post-delivery after stating that the study was too onerous, one was withdrawn from the study because her infant was diagnosed with an autosomal defect at 32 weeks gestation, and one woman was lost to follow-up after she moved interstate. Four women in the BM group, who had already completed the early childhood phase of the study with their first child, became pregnant with their second child whilst data collection for the pregnancy and neonatal phase of the study was still underway. Hospital policy required that these four mother-infant dyads were monitored throughout pregnancy and the infants monitored for NAS. However, follow-up data were not collected for these infants.

Seven women in the MM group were not available for inclusion in the early childhood phase of the study: two women were lost to follow-up, one woman was withdrawn from the study after seeking termination of her pregnancy, one woman was withdrawn from the study because she was prescribed olanzapine and sodium valproate for a previously diagnosed mood disorder (bi-

polar and schizoaffective disorder), one woman withdrew at a gestational age of 28 weeks, and one woman withdrew one week post-delivery, both stating that the study was too onerous. After completion of the pregnancy and neonatal phase of the study it was discovered that one woman in the MM group had a psychiatric diagnosis and was on medication that should have precluded her from enrolment. Although follow-up information was collected for this family, their data are not included in the analyses.

Three women in the control group were not available for inclusion in the early childhood phase of the study: one woman was withdrawn at 16 weeks gestation as she was receiving isoniazid treatment for tuberculosis exposure, one woman was withdrawn after miscarriage at a gestational age of 24 weeks, and one woman who initially attended the general antenatal clinic changed her antenatal care to midwifery group practice (MGP). Because the care provided by MGP differs from that provided by the general antenatal clinics (in that women are visited at home by a midwife rather than attending a hospital-based clinic) this woman was not eligible to continue in the study.

<u>The Early Childhood Phase</u>

Four month assessment

Of the 106 mother-infant dyads eligible to participate in the early childhood follow-up, 87 (82%) attended an appointment at the WCH ± 1 week of their infant reaching four months of age. Amongst those who did not participate, 12 families (seven in the BM group, four in the MM group, and one in the control group) could not be contacted despite exhaustive efforts. Six families (two BM, three MM and one control) did not wish to continue their involvement in the study, and one child in the MM group died of meningococcal disease. The final sample for the four month follow-up assessment consisted of 30 women maintained on buprenorphine, 24 women maintained on methadone and 33 women who were not opioid-dependent, and their infants. Two infants in the MM group did not undergo VEP assessment or have growth

measurements taken at this assessment because their families had moved too away from the study area for them to be brought into the Women's and Children's Hospital (WCH) for assessment; however questionnaires for each of these families were returned by post.

Twelve month assessment

Eighty three children and their mothers (or primary caregivers) completed the 12 month assessment (28 BM, 22 MM and 33 controls), which was 78% of the 106 eligible; and 95% of those assessed at four months. At the 12 month assessment, three children were not in the care of their natural mothers and questionnaires were completed by their primary caregivers. This was the maternal grandmother in the case of two children (one BM, one control) and the natural father in the case of the third (BM group). Three families (two BM, one MM) were lost to follow-up and one woman in the MM group withdrew her child from the study when a notification of suspected child abuse was made to Families SA (the state child protection agency) after the four month assessment. One child in the BM group did not complete a BSID-II assessment as he was too tired to participate at the scheduled time and the family could not be contacted to make another appointment, and one child in the MM group did not undergo assessment on the BSID-II as the family had moved away from the study area. All other questionnaires were completed for each of these children.

Twenty four month assessment

Seventy three children and their mothers (or primary caregivers) completed the 24 month assessment (24 BM, 19 MM and 30 controls), which was 69% of the 106 eligible; and 88% of those assessed at 12 months. At this assessment, three children were not in the care of their natural mothers and questionnaires were completed for them by their primary caregiver. This was the natural father in the case of one child in the BM group. In the control group one child was in the care of her maternal grandmother, whilst one was in state care. Ten families (4 BM, 3 MM, 3 controls) were lost to follow-up. Questionnaires were not returned by two families (one in each of

the BM and MM groups) and only their children's growth measurements and BSID-II scores were collected.

The number of participants and retention for each of the stages in the early childhood phase of the study are presented in Table 2.1.

2.5 Procedure

<u>The Early childhood phase</u>

Four month assessment

Families were telephoned approximately 14 weeks post delivery. The infant's mother or primary caregiver was asked whether they wished to continue participating in the study, and the parent was provided with a verbal description of the planned assessments. In the majority of cases, a child's primary caregiver was the natural mother, but for brevity, the term 'parent' will be used to describe a child's primary caregiver.

Parents were invited to attend an appointment at the Women's and Children's Hospital at ± 1 week of their infant reaching four months of age(chronological). Infants were assessed at a specific chronological age, rather than a corrected age, to ensure that parents had spent the same amount of time with their infants before completing the measures which incorporated questions about parenting, parent-infant attachment and infant temperament. Differences in gestational age were adjusted for in analyses. At the four month assessment parents completed the questionnaire (Appendix J), with assistance if requested, infants' neurological development was assessed using Visual Evoked Potentials (VEP) and infants' weight, length and head circumference were measured. At the end of this appointment the family's contact details were confirmed, and details of a family member or friend were collected in the event that the participant could not be contacted for the next assessment. The family was provided with a parking or taxi voucher and the $A50 reimbursement for their time; and an age-appropriate toy was given to the infant.

Twelve and twenty-four month assessments

The protocol for the assessments at 12 and 24 months was the same. Families were contacted by telephone prior to the children's first and second birthdays and invited to participate in the next stage of the study. A description of the questionnaire and developmental assessment was provided and an appropriate time to visit the family at their home or at another suitable location was arranged. I attempted to schedule visits within two weeks of a child's birthday as the BSID-II specifies sets of items to administer dependent on a child's chronological age (Bayley, 1993). Parents were informed that the visit would last from one and a half to two hours. The questionnaire was posted to the parent for completion prior to the home visit. Two contact telephone numbers were provided to parents in the event that a home visit needed to be rescheduled. If the parent was unable to be contacted by telephone, I attempted to obtain new contact details from nominated family or friends, the telephone book or online White Pages or, in the case of the MM and BM groups, via the central methadone register. If this was unsuccessful, a letter reminding the parent about the study and asking them to contact me (Appendix K) was posted to the last known address.

During the home visit the completed questionnaire booklet was collected and children's neurological development was assessed using the BSID-II item-set appropriate for their age (Bayley, 1993). For children born prematurely, the child's corrected age (chronological age minus the number of days born premature) was calculated and the BSID-II item-set appropriate for their corrected age was administered. The test is described in more detail below. Children's weight, length and head circumference were also measured at the home visit. The procedure followed is described in more detail in section 2.6.

The BSID-II was generally completed during one session. However if the child became too tired or distressed, a second appointment was arranged. At the completion of the assessment the children were praised and presented with a picture book as a token reward for their participation.

Parents were also thanked for their participation and received the $A50 as reimbursement for their time.

At the home visit I completed the Home Observation for Measurement of the Environment (HOME) Scale (Caldwell & Bradley, 1984) and recorded a general summary of the assessment. The summaries were unstructured qualitative records of the visit to the participant's home and provided contextual information about the assessments. While content of the summaries varied between visits, they provided a general comment on the child's behaviour, attention and concentration during the assessment.

After the assessment a brief report of the child's overall development was mailed to the family (Appendix L). An invitation was also provided to parents to discuss the assessment if they so wished. If a parent raised concerns about their child's development, they were provided with generic information regarding suitable services to which they could be referred (i.e. GP, Child and Youth Health, Paediatrician). Direct referral to more comprehensive assessment services was beyond my professional capabilities, and may have biased the results of future study assessments.

2.6 Measures

Table 2.2 provides a summary of data collected and measures used during each stage of the study.

<u>The Pregnancy and Neonatal Phase</u>

Sample Characteristics

Background information about mothers was collected at recruitment using a structured face-to-face interview. This included maternal age at recruitment, gestational age at recruitment, parity, gravida, marital/partner status, drug use history (including alcohol and tobacco use); and for opioid-dependent participants, maintenance treatment history and maintenance dose. Whilst information was obtained from mothers' medical records about pregnancy complications,

adverse events, and labour and delivery statistics, these results are presented elsewhere (Gordon, 2006).

Information obtained from infants' medical records included gestational age at delivery, APGAR scores at 1 minute and 5 minutes, birth growth parameters, and severity, duration and treatment of neonatal abstinence syndrome (NAS, opioid withdrawal). All infants were monitored for symptoms of NAS four-hourly until discharge using a modified Finnegan Scale (New South Wales Department of Health, 2006b) (Appendix H). This is an 18-item scale assessing the presence and severity of NAS symptoms, including central nervous system disturbances (such as tremors, poor sleeping and high pitched crying), metabolic vasomotor and respiratory disturbances (such as fever, sneezing respiratory rate) and gastrointestinal disturbances (such as poor feeding, excessive sucking and vomiting). Infants in the control group were included in this scoring because some of the items on the scale may be due to normal neonatal behaviour (e.g. yawning, sleep difficulties) or other infant health problems (fever, seizures). This modified scale is used extensively throughout Australian hospitals (New South Wales Department of Health, 2006b). It differs slightly from the original scale developed by Finnegan et al. (Finnegan, Connaughton, Kron, & Emich, 1975) in that two items regarding the Moro reflex have been omitted, as have items evaluating sweating and mottling.

The modified scale has a minimum score of 0, indicating absence of NAS, and a maximum score of 41, indicating severe NAS. Pharmacological treatment was initiated with morphine (with a starting dose of 0.5 mg/kg per day) if an infant scored ≥8 on three consecutive occasions. Dose was increased in increments of 0.2mg/kg per day, based on the infant's score (see Appendix I for treatment and weaning protocol). One infant in the BM group was treated with phenobarbitone at the mother's request and two others in the BM group were treated concurrently with morphine and phenobarbitone. Approximately half of the infants in each maintenance group

were pharmacologically treated for NAS (see Table 3.5). No infant in the control group was treated pharmacologically for NAS symptoms.

<u>The Early Childhood Phase</u>

Neurological Development

Children's neurological development was assessed at each assessment. At four months, infants' neural maturity was assessed at the Women's and Children's Hospital using Visual Evoked Potentials (VEP). At 12 and 24 months, children were assessed in their homes using the Bayley Scales of Infant Development- Second Edition (BSID-II).

Visual Evoked Potentials (VEP)

VEP elicit electrographic patterns which reflect brain development in terms of axon and dendrite growth, synapse formation and extent of myelination (Pryds, Trojaborg, Carlsen, & Jensen, 1989; Scher, et al., 1998). VEP latency provides a measure of the speed of processing from the visual stimulus to the peak of neuronal depolarisation in the primary visual cortex, and provides a sensitive and impartial indication of the maturation of the visual pathway (Madrid & Crognale, 2000; Skarf, 1989).

Binocular pattern-reversal visual evoked potentials (VEP) were recorded in a darkened room under transient conditions (during which polyphasic responses are evoked by low frequency stimuli). Infants were tested at 15-17 chronological weeks of age and were seated on the lap of a parent or caregiver. Pacifiers were used to settle infants and attention to the screen was maintained with a small toy or auditory stimulus (a bell, jingled out of view, behind the screen).

Latencies for the first 69 infants were recorded using the Enfant 4010 system (Neuroscientific Corp, Farmingdale, NY). Infants were seated in front of a 48 cm (19 inch) monitor (Neuroscientific Corp) on which high-contrast, black and white, checkerboard pattern reversal (2 Hz) stimuli were

presented for 30 second periods (Figure 2.2). The mean luminance of the stimulus display was 50 cd/m^2 (contrast 80%). Three 5 mm Grass gold cup electrodes were attached to the infants' scalp with Grass EC2 conducting paste. The active electrode was placed 1 cm above the inion (external occipital protuberance), the reference electrode at the vertex, and the inactive electrode on the forehead. Checkerboard patterns subtending two different check sizes (48 and 69 minutes of the retinal arc[1]) were presented. The viewing distance for each pattern was 50 cm, with a viewing field of 25 degrees.

Frequencies between 1-100 Hz were collected and amplified 10K using Grass PC model 511 AC amplifiers. A minimum of two recordings were performed for each check size and the latencies (measured in milliseconds) of the first positive wave (P1) for each recording were averaged for analysis. Recording was paused if the infant looked away from the screen and breaks were given if the child was tired or hungry.

The Enfant equipment was not available for assessment of the final 16 infants. As a result, latencies for these children were recorded using the Nicolet Bravo Evoked Potential system (Nicolet Biomedical, Viasys Neurocare Madison, WI). Stimuli (mean luminance 32 cd/m^2, contrast 91.9%) were presented on a 38 cm (15 inch) monitor (Nicolet) until a stable response was obtained and replicated. Infants were seated 50 cm and 75 cm in front of the stimulus screen to obtain the respective check sizes of 48 minutes and 69 minutes of arc. Electrode placement (10 mm Grass gold cup) was the same as for the Enfant equipment except for the reference electrode which was placed mid-frontal. Nicolet 16 channel EC amplifiers were used to amplify collected frequencies. Two experienced operators (one per machine), blind to participants' group status, conducted the VEP assessments.

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[1] A minute (') of arc is a unit of angular distance, with one minute equal to one sixtieth of a degree.

Equivalence testing of the VEP equipment was carried out on a test subject prior to conducting the infant VEP tests on the Nicolet Bravo system. Although the luminance and contrast differed slightly between the two pieces of equipment, recorded values were judged by two experienced technicians to be of appropriate equivalence (latencies in response to both check sizes averaged between 96.0 and 100.0 ms on each system).

Bayley Scales of Infant Development – Second Edition (BSID-II)

The BSID-II is a widely used standardised assessment which measures a child's current developmental functioning (Bayley, 1993). Designed for use with children aged between 1 month and 42 months, it is a revised version of the first edition of the scales which were based on early work by Nancy Bayley. Aspects of development such as memory, simple problem solving, language abilities, body control, coordination, and fine motor movement are tested via observations and a series of simple tasks for children. A child's performance on these tasks, together with parents' observations, yield estimates of the child's current functioning, compared to other children of their age. The BSID-II consists of three scales: the Mental Scale, Motor Scale, and Behaviour Rating Scale (BRS). For the Mental and Motor Scales, age related item-sets are administered in a flexible format and raw scores (in appropriate age categories of one-month increments), representing the total number of items successfully completed, are converted to the Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores. The MDI and the PDI were constructed to have a normalised standard score with a mean of 100 and a standard deviation (SD) of 15. The BRS is a 30-item investigator completed questionnaire assessing the child's behaviour (including attention, initiative and temperament) during the testing session. Behaviours are rated on a 5-point Likert scale; scores are summed to generate four subscale scores and a Total Behaviour Score. Scores from the BRS are primarily used to supplement information provided by the Mental and Motor Scales and assist in their interpretation.

The BSID-II test manual reports good internal consistency for the MDI, PDI and total BRS scores for a sample of 100 children at 12 months (MDI, α=.88; PDI, α=.84; BRS, α=.90) and 24 months (MDI, α=.92; PDI, α=.83; BRS, α=.91); and good test-retest stability (MDI, r=.87; PDI, r=.78) over intervals ranging from 1 to 16 days (median 4 days). Content and construct validity for the MDI and PDI is reportedly good (Bayley, 1993) and concurrent validity has been demonstrated for the BSID-II with strong correlations between the MDI and scales scores on the Weschler Preschool and Primary Scales of Intelligence – Revised (WPPSI-R) and McCarthy Scales of Children's Abilities; and moderate correlations between the PDI and the McCarthy Scales of Children's Abilities (Bayley, 1993).

In 2006, the BSID-II was developed and re-standardised as the Bayley Scales of Infant and Toddler Development – Third edition (BSID-III) (Bayley, 2006). Because the current longitudinal study was commenced prior to the availability of the BSID-III, the BSID-II was used for all assessments in order to maintain consistency of score interpretation.

Children's Temperament

At four months, temperament was assessed using the Short Temperament Scale for Infants (STSI) (Sanson, Prior, Garino, Oberklaid, & Sewell, 1987) completed by the child's primary caregiver. Temperament at 12 and 24 months was assessed using the Short Temperament Scale for Toddlers (STST) (Prior, Sanson, Smart, & Oberklaid, 1989). These 30-item questionnaires have Australian norms and were developed as part of the Australian Temperament Project (Prior, et al., 1989; Prior, Sanson, Smart, & Oberklaid, 2000). Parents respond by rating their child's recent behaviour in response to everyday activities and events on a 6-point scale (ranging from 'almost never' to 'almost always'). Higher scores reflect more difficult temperament (e.g. greater distractibility, lower persistence). Both measures are based on the model of temperament proposed by Thomas and Chess (Thomas & Chess, 1977) and used in the New York Longitudinal Study (NYLS) which conceptualises temperament as a child's disposition on nine characteristics: activity level,

rhythmicity (or regularity) of body functions, approach or withdrawal (response to new stimuli), adaptability (adjustment to new experiences), intensity of reactions (energy level of a child's response), quality of mood, persistence (or attention span), distractibility, and sensory threshold. The questionnaires are described in more detail below.

Short Temperament Scale for Infants

This scale was developed from a factor analysis of the Revised Infant Temperament Questionnaire (Carey & McDevitt, 1978). It contains five subscales, each assessing different dimensions of temperament: *Approach* measures a child's sociability and adaptability to new situations and experiences (e.g. "The baby's first reaction, at home, to approach by strangers is acceptance"); *Rhythmicity* measures the regularity and predictability of the child's usual biological functions (e.g. "The baby gets sleepy at about the same time each evening, within ½ hour") ; *Cooperation/Manageability* measures the ease with which the child adapts to everyday events (e.g. "The baby continues to fret during nappy change in spite of efforts to distract him/her with game, toy or singing, etc"); *Activity/Reactivity* refers to the amount of body movement the child usually makes, and the intensity of the child's reactions to stimuli (e.g. "The baby moves a lot, squirms, bounces, kicks, while lying awake in cot"); and *Irritability* measures the amount of the child's crying and fussing (e.g. "The baby amuses self for ½ hour or more in cot or playpen, looking at mobile, playing with toy, etc"). Acceptable internal consistency (α=.57 to .76) and test-retest reliability over a two to nine week period (*r*=.77 to .90) have been demonstrated for the infant subscales. A composite 'Easy/Difficult' Temperament Score (EDS) is calculated by averaging the Approach, Cooperation/Manageability, and Irritability scale scores. Infants scoring ≥ one standard deviation above the standardised Infant EDS mean are classified as 'difficult', while those scoring ≤ 1 *SD* below the standardised EDS mean are classified as having an 'easy' temperament (Oberklaid, Sanson, & Prior, 1986; Sanson, Prior, & Oberklaid, 1985).

Short Temperament Scale for Toddlers

The toddler version was developed from a factor analysis of the Toddler Temperament Scale (Fullard, McDevitt, & Carey, 1984). It also contains the Approach/Adaptability, Cooperation/Manageability, Rhythmicity, and Reactivity subscales (using items developmentally appropriate for toddlers aged 12 to 42 months), and includes two extra subscales measuring *Persistence*: the child's ability to focus on activities and tasks (e.g. "The child plays continuously for more than 10 minutes at a time with a favourite toy") and *Distractibility*: the ease with which a child can be distracted or comforted when required (e.g. "The child stops eating and looks when he/she hears a sudden noise, such as telephone, doorbell"). Satisfactory internal consistency (α=.56 to .85) have been reported for the toddler subscales. The STST questionnaire also yields a composite EDS, which is the mean of the Approach/Adaptability, Cooperation/Manageability, and Reactivity subscales (Prior, et al., 1989). Toddlers scoring one standard deviation above the standardised Toddler EDS mean are classified as 'difficult', while those scoring one standard deviation below the EDS mean are classified as having an 'easy' temperament (Prior, et al., 1989).

Children's Physical Development

Children's physical development was assessed via collection of anthropometric measurements at each assessment.

Anthropometric measurements

At each assessment, infants' weight, length and head circumference (HC) were measured. At the 4-month assessment infants were weighed without clothes on a calibrated Seca Baby Balance (model 727; Seca, Hamburg, Germany). Length was measured in the supine position to the nearest 0.5 cm by two individuals using an infant measuring mat. Head circumference was measured at the largest occipitofrontal circumference to the nearest 0.1 cm with a paper tape.

At the 12-month assessment, infants were weighed without clothes on a calibrated Seca Infant and Toddler Digital Scale (model 734; Seca, Hamburg, Germany). Length and HC were measured as per the 4-month assessment. At the 24-month assessment, toddlers were weighed on Soehnle bathroom scales (Soehnle Professional, Backnang, Germany). Height was measured, without shoes, on a stadiometer and HC measured as per the previous assessments.

Sample Characteristics for the Early Childhood Phase

At each assessment, information was obtained about the children's general health, sleep behaviours, current breastfeeding status, and demographic characteristics of participating families. Additionally, information was collected about psychosocial characteristics including the quality of parent-child interaction, parental psychopathology, perceived social support, the quality of the child's care-giving environment, and recent parental substance use.

Children's General Health

At each follow-up assessment parents were asked to report whether their child had experienced any medical problems since the last assessment. If they answered 'yes' they were then asked to list the medical problems. Parents were also asked whether their child had experienced any seizures since the previous assessment and whether they were febrile or afebrile.

Children's Sleep Behaviours

Information about the sleeping patterns of infants and children was collected using a questionnaire based on the Brief Infant Sleep Questionnaire (BISQ) (Sadeh, 2004). The BISQ was designed as a screening instrument for use in paediatric settings. It has been validated in a sample of 100 infants and showed significant correlations with actigraphic sleep measures (which record activity levels) and daily sleep logs. The BISQ has been shown to discriminate between children with and without sleep difficulties, and good test-retest reliability (r>.82) has been demonstrated over an interval of three weeks (Sadeh, 2004). The questionnaire used in the early childhood

phase of the study obtained information about nocturnal and daytime sleep duration, number and duration of night wakings, child's usual bed-time, time spent settling the child at night, and whether parents thought their child's sleep was a problem. It differed from the BISQ in that the questions about infants' sleeping location, sleeping position and method of falling asleep were omitted. Sadeh's cut-off scores (which do not incorporate these omitted questions) were used to identify children who were poor sleepers. The criterion for poor sleeping was defined as one or more of the following: a) waking >3 times per night; b) nocturnal wakefulness of >1 hour; or c) total sleep time (including day and night sleeps) <9 hours (Sadeh, 2004).

Breastfeeding Status

At the 4-month assessment, questions based on the World Health Organisation (WHO) definitions of breastfeeding (Webb, Marks, Lund-Adams, Rutishauser, & Abraham, 2001) were used to assess feeding status of infants. Parents were also asked whether they had introduced solid food to their child's diet. At the 12- and 24-month assessments parents reported if their child was still breastfed, or at what age breastfeeding had ceased.

Research suggests that breastfeeding has a protective effect on infant health, particularly in terms of infectious childhood illnesses, such as otitis media, respiratory tract infections and gastrointestinal infections. It has been shown that breastfeeding a child for longer confers greater protective effect against these illnesses, while exclusive breastfeeding (i.e. infant receives only breast milk) appears to have the most beneficial health effects (House of Representatives Standing Committee on Health and Ageing, 2007). Breast feeding has also been found to be associated with better developmental outcomes in full-term and premature infants. Khedr and colleagues (Khedr, Farghaly, Amry, & Osman, 2004) found that full term infants exclusively fed breast milk (n=30) had significantly shorter P1 latencies in response to flash VEPS at 12 months of age, compared with formula fed infants (n=23, $M \pm SD$=96.4±9.0 ms, p<.05)(Khedr, et al., 2004). Feldman and Eidelman (2003) found that in a group of 86 premature infants, infants receiving a

greater amount of breast milk (>75% nutrition, *n*=34) had better neurological development scores on the Brazelton Neonatal Behaviour Assessment Scale (NBAS) at 37 weeks gestational age (GA), and higher MDI and PDI scores on the BSID-II at six months corrected age (CA), than infants receiving ≤75% breast milk. Breast feeding was also associated with increased levels of positive maternal-infant interaction and decreased levels of maternal depression (Feldman & Eidelman, 2003).

Demographic Characteristics

Information about the demographic characteristics of participants was collected at each assessment using a questionnaire developed by the Research and Evaluation Unit, Children Youth and Women's Health Service, South Australia. This questionnaire obtains information about the child's age, gender, the respondent's relationship to the child, the number of dependent children in the household, the number of household moves, family structure, accommodation and annual income, as well as maternal age, and information about the educational attainment, employment status and usual occupation of the mother (or maternal figure) and father (or paternal figure) in the child's household.

Maternal Psychosocial Characteristics

Parent-Child Interaction

Parents completed two measures of parent-child interaction: The Maternal Postnatal Attachment Scale (Condon & Corkindale, 1998) at the 4-month assessment and the Parenting Stress Index (Abindin, 1995) at the 12- and 24-month assessments.

Maternal Postnatal Attachment Scale

This 19-item questionnaire, developed by Condon and Corkindale (Condon & Corkindale, 1998), was designed to assess the quality of a mother's emotional response to her infant. Mothers report on the intensity and frequency of subjective experiences regarding their infant during the

first year postpartum. It was administered to parents at the 4-month assessment. For the majority

of items parents choose from four or five responses (e.g., for the item 'When I interact with the

baby I feel…' the response options are 'very incompetent and lacking in confidence', 'moderately

incompetent and lacking in confidence', 'moderately competent and confident', and 'very

competent and confident'). For two items, parents choose from two responses (e.g., for the item

'I try to spend as much time as I possibly can <u>playing</u> with the baby', for which the response

options are 'this is true' and 'this is untrue'). Each response is recoded to a score on a 5-point

scale with higher scores indicating higher levels of attachment. The scale yields three construct

scores: Quality of Attachment, Absence of Hostility, and Pleasure in Interaction, as well as a

Global Attachment score which is calculated by summing responses to all items (range 19-95).

Internal consistency of the Global Attachment score was demonstrated in a sample of 210

mothers of 4-month old infants with α=.79. Good test-retest reliability over a 2-week test interval

was reported on a subsample of 56 women, with a significant Pearson correlation coefficient of

.86 and an intraclass correlation coefficient of .70 (Condon & Corkindale, 1998). Construct validity

of the Global Attachment score was evaluated with the same sample of mothers. Global

Attachment scores were found to be significantly related to infant temperament, levels of

maternal social support, and maternal psychopathology (Condon & Corkindale, 1998).

Parenting Stress Index

The Parent Domain subscale of the Parenting Stress Index (PSI) (Abindin, 1995) was administered

to parents at the 12- and 24-month assessments. This self-report measure is designed to identify

stressful parent-child systems which may relate to dysfunctional parenting and later child

emotional and/or behavioural problems (Abindin, 1995). The 120-item PSI has been standardised

for parents of children aged one month to 12 years. It yields total scores and a number of

subscale scores within separate Child and Parent Domains, as well as a Total Stress score and a

Life Stress score. Only the Parent Domain scores were used in the present study as the other

scales were not considered pertinent.

The PSI Parent Domain is comprised of 54 items relating to parental functioning, from which seven subscales can be calculated: *Competence* measures a parent's feelings of capability in fulfilling the parenting role (e.g. 'I feel capable and on top of things when caring for my child'), *Isolation* measures the extent to which the parent feels socially isolated, *Attachment* measures the parent's feelings of emotional closeness to the child (e.g. ' My child knows I am his or her parent and wants me more than other people'), *Health* assesses the parent's physical health (e.g. Physically, I feel good most of the time'), *Role Restriction* measures the extent to which the parent views their parenting role as restricting them in terms of maintaining their own identity (e.g. 'I feel trapped in my responsibilities as a parent'), *Depression* assesses feelings of unhappiness or guilt (e.g. 'I feel every time my child does something wrong, it is really my fault') and *Spouse* measures feelings of emotional and practical support from the other parent (e.g. 'Having a child has caused more problems than I expected in my relationship with my spouse (or male/female friend)'). For the majority of questions, parents rate their level of agreement on a 5-point scale (ranging from 'strongly agree' to 'strongly disagree'), with statements about child and parent characteristics and family context. A Parent Domain Total score is calculated by summing the seven subscale scores. Higher scores indicate greater levels of dysfunction. The Parent Domain subscales of the PSI have a demonstrated satisfactory degree of internal consistency (α=.70 to .84), and good test-retest reliability across time intervals between 1- and 12-months (r=.69 to .91). Adequate levels of construct validity have been reported, with Parental Domain scores significantly correlated with BSID scores, quality of parent-child attachment and maternal psychological distress (Abindin, 1995).

Parental Psychopathology

Parents completed two measures of parental psychopathology: the Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden, & Sagovsky, 1987) at the 4-month assessment, and the 28-item version of the General Health Questionnaire (GHQ-28) (Goldberg & Hillier, 1979) at all three assessments.

Edinburgh Postnatal Depression Scale

The Edinburgh Postnatal Depression Scale (EPDS; (Cox, et al., 1987) is a 10-item self-report

screening tool widely used for the identification of postnatal depression (PND)(Boyce, Stubbs, &

Todd, 1993; Eberhard-Gran, Eskild, Tambs, Opjordsmoen, & Samuelsen, 2001; B. Edwards,

Galletly, Semmler-Booth, & Dekker, 2008; Matthey, Henshaw, Elliott, & Barnett, 2006; McMahon,

Barnett, Kowalenko, Tennant, & Don, 2001; Murray & Carothers, 1990; Patel, et al., 2003). The

EPDS is comprised of items assessing common symptoms of postnatal depression (including

anhedonia, anxiety, panic, insomnia due to unhappiness, sadness, tearfulness and self-harm)

experienced within the previous 7 days. Participants respond to statements on a 4-point scale (0-

3). For example, for the first item, 'I have been able to laugh and see the funny side of things',

participants choose from one of the following four responses, a)'As much as I always could', b)

'Not quite so much now', c) 'Definitely not so much now', d)'Not at all'. A total EPDS score ranging

from 0 to 30 is calculated, with higher scores indicating greater severity of symptoms.

The EPDS has been validated in a sample of 103 Australian women using a cut-off score of 12.5

which yielded 100% sensitivity, a specificity of 95.7% and positive predictive value of 50% (Boyce,

et al., 1993). A recent Australian study (Matthey, et al., 2006) has highlighted the increasing use of

unvalidated cut-off scores in published studies using the EPDS and the use of potentially confusing

wording to describe scores indicating 'caseness'. On the recommendation of these authors, the

current study uses the validated score of '10 or more' for reporting at least probable minor

depression and '13 or more' for reporting on probable major depression (Matthey, et al., 2006).

General Health Questionnaire

The General Health Questionnaire (GHQ; (Goldberg & Hillier, 1979) is a widely used self-report

screening tool for the detection of psychological distress in community populations (Donath,

2001). Participants rate themselves, on a 4-point scale, according to the degree to which they

have experienced symptoms over the past few weeks. The GHQ asks about changes in normal

functioning rather than assessing the presence of chronic disorders.

The 28-item version of the questionnaire (GHQ-28) was completed by parents at each follow-up

assessment. Four subscales are calculated for this version of the questionnaire: Somatic

Symptoms (e.g. 'Have you recently been feeling perfectly well and in good health?'), Anxiety and

Insomnia (e.g. 'Have you recently lost much sleep over worry?'), Social Dysfunction (e.g. 'Have

you recently been managing to keep yourself busy and occupied?'), and Severe Depression (e.g.

'Have you recently been thinking of yourself as a worthless person?'); along with a Total score

which is calculated by summing all 28 items. The standard binary 'GHQ scoring method' (0-0-1-1),

as advocated by Goldberg (Goldberg et al., 1997; Goldberg & Hillier, 1979), was employed for this

study. Item responses indicating the presence of psychopathology were scored as 1. Total scores

for the GHQ-28 range from 0 to 28 and higher scores indicate higher levels of psychological

distress. Concurrent validity for the GHQ-28 has been demonstrated with the Total score

correlating with independent clinical assessment (α=.32-.76) (Goldberg & Hillier, 1979). The GHQ-

28 has shown acceptable levels of sensitivity (79.7%), specificity (79.2%) and positive predictive

value (54.7%) across a sample of over 5000 participants in 15 general health care centres

(Goldberg, et al., 1997).

The scale's author recommends using a total threshold score of 4/5 to indicate the likelihood of

significant levels of psychological distress (Goldberg & Hillier, 1979). However, in the WHO study

of psychological disorders in general medical settings, Goldberg and colleagues (1997) found that

the average threshold score across all 15 centres (and 10 different languages), was 5/6, with a

threshold of 6/7 for a Manchester, UK sample (Goldberg, et al., 1997). Studies using the GHQ with

postpartum women recommend using a raised threshold score due to sleep disturbances and

physical symptoms that may be related to the post-natal period (Boyce, et al., 1993; Nott & Cutts,

1982; Skari et al., 2002; Watson & Evans, 1986). A threshold score of ≥6 (Skari, et al., 2002) was used to indicate a significant level of psychological distress for the purpose of this thesis.

Social Support

Parental social support was measured at each assessment using the Interview Schedule for Social Interaction -Short Form (ISSI-SF) (Unden & Orth-Gomer, 1989).

Interview Schedule for Social Interaction-Short Form

This 30-item self-report instrument is an adaptation of the Interview Schedule for Social Interaction developed by Henderson, Duncan-Jones, Byrne and Scott (1980). It assesses subjective perceptions of one's social support network (including close relationships, friends, colleagues and acquaintances), in particular, the availability and perceived adequacy of social integration and attachment (Persson & Ørbæk, 2003; Thernlund & Samuelsson, 1993). The ISSI-SF yields four subscales: availability of attachment (AVAT; with a maximum obtainable score of 6), adequacy of attachment (ADAT; with a maximum obtainable score of 10), availability of social interaction (AVSI; with a maximum obtainable score of 6) and adequacy of social interaction (ADSI; with a maximum obtainable score of 8). A Total social support score is derived by summing all of the items (Eklund, Bengtsson-Tops, & Lindstedt, 2007; Thernlund & Samuelsson, 1993). Higher scores indicate better perceived social support.

High internal consistency of the ISSI-SF (α=.84-.91) has been demonstrated in a sample of 297 Swedish mental health patients (Eklund, et al., 2007) and it has been shown to distinguish between respondents with high and low trait anxiety, and social desirability scores (Persson & Ørbæk, 2003). Good test-retest reliability (over a six week interval) was reported for the Total score in a sample of staff members from a Swedish child psychiatric clinic (α=.87); however stability of scores was lower (α=.45) in a community group of parents over the same interval (Thernlund & Samuelsson, 1993). Adequate levels of construct validity have been reported in an

Australian sample, with the Total ISSI-SF scores significantly correlated with greater parental psychological distress (α=-.51); however correlations were lower (α=-.22 to -.35) with parent-rated child temperament scores in the same sample (Miller-Lewis et al., 2006).

Care-giving Environment

Evaluation of the child's care-giving environment was undertaken at the home visits, during the 12- and 24-month assessments, using the Infant version of the Home Observation for Measurement of the Environment (HOME) Inventory (Caldwell & Bradley, 1984).

The Infant HOME Inventory

This is a 45-item instrument designed to evaluate the quantity and quality of social, emotional and cognitive experiences available to infants in their own home. Each item is scored dichotomously (yes/no) with the inventory yielding six subscales: Parental Responsivity (e.g. 'Parent spontaneously praises child at least twice'), Acceptance of Child's Behaviour (e.g. 'Parent does not scold or criticise child during visit'), Organisation of the Environment (e.g. 'Child has a special place for toys and treasures'), Provision of Appropriate Learning Materials (child has a range of learning materials e.g. 'Cuddly toy or role-playing toys', ' Toys for literature and music'), Parental Involvement with Child (e.g. 'Parent keeps child in visual range, looks at often') and Variety in Experience ('Child eats meals with parent and/or other children'). A Total HOME score is calculated by summing the scores of the six subscales. Total scores range from 0 to 45 with higher scores indicating a more optimal home environment (Caldwell & Bradley, 1984). Information needed to score items on the scale is obtained via a combination of observation and interview questions.

The HOME Inventory has been used extensively in developmental research (Bradley, 1994). Total HOME scores have been shown to be significantly associated with birth weight and cognitive function in children aged 2 to 13 years (Tong, et al., 2006) and moderately correlated with

perceived level of social support in new mothers ($r=.43$ to .50) (Bradley, 1994). HOME scores have also been correlated with cognitive outcomes at 5 and 6 years of age of children whose mother's smoked during pregnancy (Fried, O'Connell, & Watkinson, 1992). Internal consistency Kuder-Richardson coefficients for the scale scores have been reported to range from $r=.44$ to .89 with a coefficient of $r=.89$ for the Total HOME score in a sample of middle-class North American children aged 4 to 36 months (Caldwell & Bradley, 1984). Slightly lower coefficients for the subscale scores ($r=.31$ to .66) and the Total HOME score ($r=.84$) were reported for a sample of lower-middle class Costa Rican children aged 13 to 24 months (Lozoff, Park, Radan, & Wolf, 1995). Concurrent and predictive validity has been demonstrated with the Total HOME score being low to moderately correlated ($r=.06$ to .30) with the MDI of the BSID in infancy, and moderately associated with WPPSI scores at 5 years of age ($r=.28$ to .53) in these two samples (Lozoff, et al., 1995).

Parental Substance Use

Information about parental substance use was collected using a questionnaire developed for this purpose by Drug and Alcohol Services South Australia (DASSA). This questionnaire asks about licit and illicit use of substances in the month prior to the assessment, as well as the parents' use of substances since the previous assessment. Information collected included type of maintenance drug (if applicable), dose, and timing of doses over the past three days. Respondents were also asked whether they had used any of the following classes of drugs: tobacco, alcohol, heroin, other opioids, marijuana, amphetamines, inhalants, benzodiazepines. For each substance that a parent indicated they had used, they were asked to report the specific substance (e.g. for 'amphetamines', this could have been cocaine, ecstasy, methamphetamine etc), how it was taken (e.g. orally, inhaled, intravenously etc), the number of days on which they had used it, and the number of times used per day on the days they had used it. For tobacco, alcohol and marijuana parents were asked about the respective number of cigarettes, drinks or cones/bongs they had used on the days they reported using each substance. Parents were also asked to indicate if they

had used any other over-the-counter or prescribed medication (including vitamins, supplements and pain relief).

2.7 Statistical Analyses

Analyses were conducted using Stata/IC 10.0 (StataCorp LP, College Station Texas) and a Type 1 Error of .05 was used for significance testing in analyses, except when stated otherwise. An overview of the statistical analyses employed in the thesis is described in this section with further details provided in individual results chapters.

Mean scores and standard deviations (*SD*), or median scores and observed ranges, were calculated for continuous variables and frequencies were calculated for categorical variables. One-way between groups analyses of variance (ANOVA) were conducted to test for statistically significant differences in mean scores between the three groups on normally distributed continuous outcome measures. Post hoc tests using the Bonferroni adjustment procedure were employed to examine the locus of any differences between the groups. Non-normally distributed variables were transformed when appropriate. For variables where a suitable transformation could not be found, Kruskal-Wallis equality-of-populations rank tests were used to examine statistically significant differences in median scores between the three groups. Mann-Whitney U tests were conducted to evaluate pair-wise differences between the three groups of infants.

A series of simple linear regression analyses (for continuous measures) and ANOVAs (for categorical measures) were conducted to examine the contribution of individual potentially confounding variables to each of the dependent outcome variables. Each bivariable model was examined for normality and constant variance, and data transformations were applied if these assumptions were not met. Non-parametric techniques were employed when a suitable transformation could not be found. Standardised coefficients (β) are reported for continuous measures.

The 21 variables which were examined for their potential to confound comparisons between the three groups were chosen from a number of theoretically appropriate maternal and infant characteristics that were collected at enrolment, throughout pregnancy, post-natally and at the 4-month follow-up assessment. Variables from Tables 3.9 to 3.9 were used as covariates when they differed significantly between groups, were associated with a given outcome at $P \le .05$, and were not highly correlated ($r > .70$) with other covariates. Variables were excluded if there were too few responses in a category for analysis to be meaningful (i.e. ethnicity) or if they were defined by group status (i.e. heroin use). In the case of scale scores, only total scores were examined. Independent variables examined were maternal age at enrolment, self-reported use of tobacco, alcohol, other opioids, marijuana, benzodiazepines and antidepressant medication during pregnancy, infant gender, gestational age at delivery, length, weight and HC at birth, method of feeding at four month follow-up (receiving some breast milk versus no breast milk), number of parental figures in the infant's household, number of children living in the household (≤ 3 versus 4 or more), education level of primary caregiver, family income category, family accommodation, maternal postnatal attachment total score at four month follow-up, GHQ total score at four month follow-up and ISSI total score at four month follow-up. On the basis of theoretical criteria (described in Chapter 1), in addition to those variables listed above, infants' mean Finnegan score, infants' corrected age, and Sadeh's sleep category (poor sleeper = yes/no) at four month follow-up were examined in relation to the four month dependent variables. The PSI Parent Domain total score and Total HOME Inventory score were examined in relation to the 12- and 24- month dependent variables. It has been suggested that child cognitive function may be influenced by environmental changes (Wilson, 1989), therefore analyses utilised the PSI and HOME scores collected at the relevant assessment. Only results for the variables that were significantly associated with individual dependent variables at $p <.05$ are presented in this thesis.

Standard multiple regression analyses were then conducted to examine the contribution of each potentially confounding variable to the individual dependent variables, whilst adjusting for the

effect of the other variables in the model. Variables were chosen for inclusion in the multivariable models if they were theoretically appropriate and had a significant bivariable relationship with the dependent variable at p <.05. Each model was examined for multicollinearity, normality of residuals and equality of variance. Data were transformed using suitable techniques if these assumptions were not met.

Finally, a series of split-plot analyses of variance (also known as mixed between-within subjects ANOVAs) were undertaken to examine whether there was a change in each of the dependent measures over time and whether changes over time varied between infants in each of the three groups. Split-plot designs can be "…used to test for differences between two or more independent groups while subjecting participants to repeated measures. The dependent variable is continuous and is measured for each group across each level of the repeated factor" (Vicky, 2009). A split-plot ANOVA design was chosen over mixed-effects models, as the latter usually require large sample sizes in order to verify assumptions about the variance-covariance structure of repeated measures.

Power analyses

The dependent outcome variables of principle interest in this study were:

- P1 latencies in response to the 48 min arc visual stimulus, measured at four months

- P1 latencies in response to the 69 min arc visual stimulus, measured at four months

- Bayley Scale Mental Developmental Index Score, measured at 12 and 24 months

- Bayley Scale Psychomotor Developmental Index Score, measured at 12 and 24 months

- Bayley Scale Behavior Rating Scale Score, measured at 12 and 24 months

- 'Easy/Difficult' Temperament Score, measured at four, 12 and 24 months

- Weight, Length and Head Circumference, measured at four, 12 and 24 months

Given the extended data collection period (2002-2006) due to difficulty recruiting a large enough

sample, post hoc power analyses, using nQuery Advisor (Statistical Solutions, Boston, MA), were

calculated for the two drug-exposed groups of infants. Table 2.3 shows the observed n for the BM

and MM groups for each of the dependent outcome variables. Presented for each dependent

variable is: (1) the mean score for the BM and MM groups, (2) the observed difference in mean

scores, (3) the effect size of the observed analysis and (3) a calculation of the n required for each

group in order to detect the observed difference with 80% power. Table 2.3 indicates that the

majority of analyses were under powered, given the restricted sample size; although some

differences were so small that they may well have become insignificant with any sample size. It is

therefore recommended that results of the current thesis should be viewed with caution and

treated as preliminary. Whilst this is the first study to describe development past the neonatal

period in detail for infants prenatally exposed to buprenorphine, any clinically relevant trends in

the data should be further examined and replicated in a larger sample.

CHAPTER 3

Sample Characteristics

This chapter describes the characteristics of families participating in the follow-up assessments of the longitudinal study. First, maternal characteristics at enrolment are described followed by information on maternal drug use reported during pregnancy. Infant characteristics at birth, Finnegan scores and treatment of neonatal abstinence syndrome are then presented. Characteristics of participating infants and families at the four month follow-up assessment are described, including socio-demographic information, infant sleep and maternal psychosocial factors.

Statistical analyses

Prior to analyses, the distributions of the variables were examined for normality and homogeneity of variance. Transformations were employed if an appropriate technique could be found. For normally distributed continuous data, one-way analyses of variance (ANOVA) were conducted to test the statistical significance of differences between means across the three groups. Post hoc tests using the Bonferroni procedure were employed to determine the statistical significance of differences between pairs of groups. Kruskal-Wallis tests were used to examine differences between groups if data did not meet the assumptions for parametric analyses. Chi square analyses and Fisher's exact tests (for variables of low frequency) were used to examine the differences between groups for categorical variables.

3.1 Maternal characteristics at enrolment

The three groups of participants were statistically comparable in terms of maternal age, gravida (first pregnancy versus second or more), parity (first born infant versus second or more), and use

of tobacco and alcohol (yes/ no) within the month prior to enrolment. Table 3.1 shows the maternal characteristics of the sample at enrolment.

Participating women were aged between 15 and 40 years ($M \pm SD$=27.45±5.94) at the time of enrolment, with the control group being on average almost two years younger than women in the other two groups. Seventy six percent of women had had a previous pregnancy ($M \pm SD$=3.15±2.05, range=1-9 pregnancies). Women in the two maintenance groups were more likely to be multigravid compared with women in the control group. The number of children a woman had delivered, prior to the current pregnancy, ranged from 0 to 5 ($M \pm SD$=0.90±1.15). Women in the control group were slightly more likely to be primparous than women in the other two groups. Eighty nine percent of participants reported smoking tobacco in the month prior to enrolment, with 84% (64/76) reporting that they smoked daily. Women in the control group were less likely than women in the other two groups to have smoked tobacco in the month prior to enrolment. Forty two percent of the sample reported consuming alcohol on at least one day in the month prior to enrolling in the study. Women in the MM group were the least likely to report consuming alcohol, with only one third reporting alcohol use in the month prior to enrolment. Half of women in the BM group reported drinking alcohol on at least one day in the month prior to enrolling in the study.

Gestational age at enrolment ranged from 4 to 35 weeks ($M \pm$SD=18.79±6.68), with the control group enrolled significantly later in their pregnancies than women in either of the two maintenance groups. This difference in gestational age at enrolment arose because potential controls were recruited from a large pool of women attending the general antenatal clinics at the WCH. They were approached to participate only after their case notes had been reviewed for eligibility by a research assistant. Potential BM and MM participants were identified by medical staff from DASSA services or the specialist antenatal clinics when they first attended for an appointment, usually early in their pregnancy.

The majority of women enrolled in the study were Caucasian, with one woman in each group reporting Asian ethnicity, and one in each of the BM and MM groups identifying as being of Aboriginal or Torres Strait Islander (ATSI) origin (Table 3.1).

The characteristics of the participating sample (n=87) were also compared, using independent samples t-tests and Fisher's exact tests, with those of the women who did not participate in the early childhood phase of the study (n=19, Table 3.2). There were no significant differences in terms of maternal characteristics at enrolment between participants and non-participants; however, participating women were on average two years older than non-participants [$F(1,103)=1.46$, $p=.23$], were more likely to be primigravid (23% versus 17%, Fisher's exact test $p=.76$) and to have had no previous children (49% versus 33%, Fisher's exact test $p=.30$). Women who continued their participation in the early childhood phase of the study were also more likely to report drinking alcohol in the month prior to enrolment in the study (45% versus 28%, Fisher's exact test $p=.20$).

In terms of other maternal characteristics, gestational age at enrolment did not differ between participants and non-participants. There were a significantly higher proportion of Caucasian participants than non-participants, with 28% of non-participants identifying as being of ATSI or 'other' origin, compared to 6% of participants who identified as Asian or ATSI.

3.2 Maternal substance use reported at enrolment and during pregnancy

Reported heroin use and maintenance therapy history

Table 3.3 summarises the heroin use and maintenance therapy history of the women participating in the study. The data for age at first heroin use was positively skewed and was normalised with a square root transformation. Although there was no significant difference between the ages at which women in the maintenance groups had first used heroin, women in the MM group were approximately 18 months younger than women in the BM group when they used heroin for the

first time (Table 3.3). The overall mean reported age at first heroin use for women in the two maintenance groups ($M \pm SD$=18.68±3.29 years, range=13-28 years) is considerably younger than that reported by the 2007 National Drug Strategy Household Survey which found that for Australians aged ≥14 years the average reported age at first heroin use was 21.9 years (Australian Institute of Health and Welfare, 2008). The majority of women in the maintenance groups (94%) had used heroin on a daily basis, and reported beginning daily use approximately 12 months after first using heroin. Two women in the control group reported using heroin approximately 10 years prior to enrolment in the study; but neither had used it on a daily basis or had ever sought treatment for heroin use. Data for the length of consistent heroin use and for average daily heroin use prior to commencing maintenance therapy were both positively skewed. For comparative purposes, length of heroin use was transformed using a power 0.4 transformation (i.e. the score multiplied by itself 0.4 times); while a square root transformation was employed for average daily heroin use. Women in the MM group reported a greater average length of consistent heroin use and slightly higher daily heroin use prior to commencing maintenance therapy than women in the BM group, although neither difference reached statistical significance. The length of time women had been on their current episode of opioid maintenance therapy was examined using a Kruskal-Wallis test. Length of maintenance therapy did not differ significantly between the two groups. The overall mean length of treatment was 12.90 months (SD=17.85 months); with women in the MM group reporting beginning maintenance therapy approximately six months earlier than women in the BM group.

The majority of women in the BM and MM groups (40/54, 74%) were already participating in maintenance therapy when they became pregnant. All women taking buprenorphine were taking it in the form of the sublingual tablet, Subutex®. A small number were not participating in a treatment program at the time of conception and started treatment with BM or MM at enrolment into the study. No physical anomalies, attributable to MM or BM were noted in any of the infants

(Gordon, 2006). Gestational ages at commencement of maintenance treatment in these women ranged from 6 to 28 weeks for the eight BM women and 3 to 18 weeks for the six MM women. When examined with Fisher's exact test, there was no significant difference between the MM and BM groups in the number of women who commenced maintenance treatment on enrolment into the study (and thus after conception) compared with those who commenced treatment prior to conception (Fisher's exact test, p= 1.00). Neither was there a significant difference between the two groups in terms of the mean number of weeks that infants were exposed to a maintenance therapy *in utero* (BM=34.4±9.7, MM=36.8±4.0, [$F(1,50)$=1.17, p=.28]). The mean maintenance medication dose reported during pregnancy was 7.3 mg (SD=4.3, range= 0.4-20.0 mg) for the BM group and 44.3 mg (SD=20.1, range= 15.0-100.0 mg) for the MM group, both of which are relatively low by current clinical standards. It has been suggested that 8 mg of buprenorphine is approximately equivalent to 60 mg methadone. On this basis, the mean doses reported in the present study are of a similar magnitude (Ling & Wesson, 2003).

Eighty three percent of women in the maintenance groups had undertaken at least one previous episode of opioid-maintenance therapy with methadone or buprenorphine prior to their current treatment episode. There was no difference between the number of women in the BM or MM groups who had previously tried maintenance therapy with methadone [$F(1,27)$=0.18, p=0.68] (range=1-5 previous treatment episodes) or buprenorphine [$F(1,19)$=0.17, p=0.69] (range=1-6 previous treatment episodes).

Self reported substance use during pregnancy

Table 3.4 provides a précis of mothers' self-reported substance use during pregnancy. A summary of the antenatal random urine drug screen results is also shown. Ninety percent (78/87) of participating women reported smoking tobacco during their pregnancy. This is considerably higher than the 18% of women who smoked during pregnancy as reported in the South Australian pregnancy outcome report for 2006 (Chan, Scott, Nguyen, & Sage, 2007), but comparable to the

85% of opioid-dependent women in New South Wales who reported smoking during pregnancy (Burns, Mattick, & Cooke, 2006). The proportion of women in this study who smoked tobacco daily (74%, 64/87) is also higher than the overall national average of 15.2% for all Australian females aged ≥14 years (Australian Institute of Health and Welfare, 2008). In the present study, a significantly greater percentage of smokers in the MM group (100%) reported smoking tobacco daily compared with smokers in both the BM (82%) and control groups (74%, Fisher's exact test p=.02). For women in this study, the average number of cigarettes smoked per day was 12 (SD=7.5, range 0.5-30 cigarettes) with the control group reporting smoking fewer cigarettes per day than women in both the BM and MM groups. While the proportion of women reporting use of tobacco in the current study is substantially higher than would be expected in a community sample (i.e. 90% vs. 18% in the 2006 South Australian pregnancy statistics sample) the high rates of smoking observed for the substance dependent groups is consistent with other research (Burns, et al., 2006; Choo, Huestis, Schroeder, Shin, & Jones, 2004; Jones et al., 2009; Kahila, Saisto, et al., 2007; Kakko, et al., 2008; Ross et al., 2005), and, in an attempt to obtain a relatively homogeneous sample, pregnant non opioid-dependent women who were smokers were specifically targeted for the control group.

Sixty percent (52/87) of women reported drinking alcohol on at least one occasion during pregnancy. The mean number of days that women reported drinking alcohol during pregnancy was 2.24 (SD=2.37, range= 1-16 days), with a mean of 1.40 drinks (SD=1.02, range=0.5-10 drinks) consumed on those days. The pattern of alcohol consumption was similar across the three groups of participants.

Women were also asked about recreational use of other substances during the antenatal period. Forty six percent of women in the maintenance groups (25/54) reported using heroin during their pregnancies (15 BM, 10 MM). The mean number of days that women reported heroin use did not differ significantly between the BM and MM groups [overall $M\pm SD$=5.80±7.78, range= 1-30 days,

F(1,91)=1.19, *p*=.27]. There were no statistically significant differences between the three groups in terms of maternal self-reported use of tobacco, alcohol, other opioids, amphetamines, hallucinogens or prescribed antidepressant medication during pregnancy, although it must be noted that the power to detect significant differences with the numbers in the current sample is limited (Table 3.4).

Seven controls reported use of other opioids, and four reported use of benzodiazepines during the antenatal period. Codeine and Kapanol® were the most commonly reported other opioids used by control subjects and temazepam was the most commonly reported benzodiazepine. While it was not reported whether these substances were used licitly or illicitly, most control subjects reported using other opioids or benzodiazepines on only one or two days during the antenatal period, suggesting that they may have been used for legitimate medical reasons rather than recreationally. Nine women in each of the MM and BM groups reported use of other opioids during pregnancy. Opioids reportedly used were codeine, Kapanol®, morphine, and 'other'. Most of these women reported taking the substance orally and on fewer than five occasions. One woman in the MM group reported injecting both morphine and Kapanol® on more than one occasion during her pregnancy, while another in the MM group reported use of an opioid on 10 days within the month prior to enrolment (substance and route of administration was not reported). One woman in the BM group reported injecting an opioid twice a day on a daily basis within the month prior to enrolling in the study. Twelve women in each of the BM and MM groups reported use of benzodiazepines during pregnancy. Diazepam was the most commonly used benzodiazepine reported by MM and BM women, with use of temazepam and alprazolam also being reported. All women reported taking the substances orally. The majority of women in the BM and MM groups reported using a benzodiazepine on fewer than 10 days during their pregnancy, with frequency of use on days used averaging between one to four times per day. The mean number of days during pregnancy on which benzodiazepines were reportedly used by

women in the maintenance groups was 18.81 (*SD*=34.14, range= 1-143 days). Again, it was not reported whether benzodiazepines were used licitly or illicitly, however some women reported that they had previously been diagnosed with anxiety or depression and may have been legitimately prescribed these medications.

Overall, 55% (48/87) of women reported use of cannabis during pregnancy (Table 3.4), over half of whom (n=25) reported using it daily. Women in the BM group were the most likely to report daily use of cannabis (45%) compared with women in either the MM (33%) or the control groups (14%, Fisher's exact test, *p*=.04). The 2007 National Drug Strategy Household Survey (Australian Institute of Health and Welfare, 2008) showed that 30% of Australian females aged ≥14 years reported using cannabis in their lifetime while 12.3% reported using cannabis on a daily basis. While the overall level of cannabis use observed in this sample is substantially higher than the reported national average (Australian Institute of Health and Welfare, 2008), the proportion of women in the control group who reported cannabis use is relatively representative of the national average. The high rate of cannabis use in the two maintenance groups is consistent with the report from the 2007 National Drug Strategy Household Survey that between 30% and 66% of recent users of illicit opioids (including heroin, non-prescription methadone and other opioids) had used cannabis concurrently (Australian Institute of Health and Welfare, 2008).

Urine drug screen results during pregnancy

Table 3.4 also shows the percentage of women in each group with a positive drug screen during pregnancy for opioids, benzodiazepines or cannabinoids. Urine samples were routinely screened for opioids, cannabinoids, benzodiazepines, sympathomimetic amines, barbiturates and cocaine. No woman had a positive screen for barbiturates or cocaine during pregnancy. Results of the sympathomimetic amine screens are not included in the analyses because women across all groups were taking medication for reflux, some preparations of which contain ranitidine which is known to produce a positive sympathomimetic amine drug screen result (personal

communication, B Davies, March 27, 2009). Because further detailed analysis of positive urine

screens was beyond the resources of the current study it was not possible to distinguish between

licit and illicit forms of sympathomimetic amines. Thus, the urine drug screen results presented

are for opioids, benzodiazepines and cannabinoids only.

There was no significant difference between the number of women in the BM and MM groups

with a positive drug screen during pregnancy (Fisher's exact test p=.77). Eight women in the

control group had a positive screen for cannabinoids during pregnancy which is consistent with

self-reported cannabis use amongst this group. Three controls had a positive screen for opioids

during pregnancy, and two had a positive screen for benzodiazepines. While it was not possible to

determine whether these substances were used licitly or illicitly, the positive screens for women

in the control group were consistent with self-reported use of these substances.

3.3 Infant characteristics at birth

Table 3.5 displays the neonatal characteristics of infants in the study. Half (43/87) of the infants in

the study were male. Gestational age at delivery ranged from 33 to 41 weeks (M=38.6, SD=1.9).

The distribution of the gestational age data was negatively skewed; therefore a power 4

transformation (i.e. the score multiplied by itself four times) was used to test differences in

analyses. The majority of infants (89%) were born at term ($\geq$ 37 weeks gestation). The mean

weight at birth was 3041 g (SD = 543, range = 1800 g - 4360 g) with 16 infants being of low birth

weight [<2500 g, (Chan, et al., 2007; Laws & Hilder, 2008)]. There was a significant difference

between the MM and control groups in terms of infant birth measurements, with MM infants

significantly more likely to be lighter at birth, to be shorter, and to have smaller head

circumferences. Birth measurements did not differ significantly between the BM and MM groups

or between the BM and control groups (Table 3.5). Simple linear regressions revealed that, after

adjusting for gestational age, a significant main effect of prenatal exposure to methadone

remained for all three birth growth measurements (see Appendix M). Apgar scores at 1 minute post delivery ranged from 4 to 10, while 5 minute Apgar scores ranged from 6 to 10.

3.4 Finnegan scores and Treatment of Neonatal Abstinence Syndrome

All infants were scored on a modified Finnegan scale for signs of neonatal abstinence syndrome (NAS). Control infants were included in this scoring because some of the items on the scale may be attributable to normal neonatal behaviour (e.g. yawning, sleep difficulties) or other infant health problems (e.g. fever, seizures). The overall mean Finnegan score was 2.90 (*SD*=1.83, range= 0-21) suggesting that infants in the study experienced only very low levels of NAS symptoms. As expected, one-way ANOVA using the transformed (square root) mean Finnegan scores showed that control infants were scored significantly lower on the Finnegan scale than infants in either of the BM or MM groups (see Table 3.5). Mean Finnegan scores did not differ significantly between the two maintenance-exposed groups of infants, indicating that infants in these two groups experienced similar levels of NAS. However, the average maximum and range of Finnegan scores obtained by infants was greatest in the MM group, suggesting that individual infants in the MM group experienced greater severity of NAS symptoms than individual infants in the BM group. As expected, the maximum and range of Finnegan scores obtained by infants in the control group was lower than that of infants in either of the maintenance groups.

Forty eight percent of infants in the maintenance groups (26/54) were pharmacologically treated for NAS. There was no significant difference between the two maintenance groups in terms of proportion of infants pharmacologically treated for NAS (see Table 3.5). Thirteen infants in the BM group and 12 in the MM group were treated with morphine. One infant in the BM group was treated, at the mother's request, with phenobarbitone only, and 2 others in the BM group were treated concurrently with morphine and phenobarbitone.

3.5 Characteristics of participating infants and families at four month follow-up assessment

Information about the demographic characteristics of participating infants and families was collected at the four month follow-up assessment (Table 3.6). At four months of age over half of the infants in the study were no longer breastfed. Almost half of all infants had experienced at least one medical problem since birth. The most frequently reported medical problem was an upper respiratory tract infection (including otitis media and fever, n=15), followed by skin rash (including thrush and eczema, n=7). At four months of age no infant in the study had experienced a seizure.

In terms of infant sleeping behaviours, 21% of the total sample was classified as having poor sleep according to Sadeh's criteria. Poor sleeping was defined as one or more of the following: a) waking >3 times per night; b) nocturnal wakefulness of >1 hour; or c) total sleep time (including day and night sleeps) <9 hours (Sadeh, 2004). The proportion of infants in each group who were classified as poor sleepers did not differ between the groups, and the majority of parents (80/87, 92%) reported that they did not consider their child's sleep a problem.

Just over half of the infants in the study were the only child living in their household (53%). Previous research has indicated that large family size is a risk factor for poorer child cognitive development and mental health (Nair, et al., 2003; Sameroff, 1998; Sameroff, et al., 1987), and that substance using mothers are more likely to be mulitgravid and multiparous compared with non-using women (Ostrea, Ostrea, & Simpson, 1997). This was not the case in the present study where four families in the control group and only two families in each of the BM and MM groups had four or more children (including the child in the study) living in the household.

The majority of infants (75%) lived in two-parent families and all, but one, were in the care of their natural mothers (this infant in the BM group was in the care of his natural father). Infants in the BM and MM groups were more than twice as likely to be living in a single parent family as

infants in the control group. Although not reaching statistical significance at the *p*<.05 level in the current study, the observed differences in family structure may be statistically significant if re-examined in a larger population.

More than half of all infants had at least one parent who had not completed secondary schooling. The MM group had a higher proportion of parents who had not completed secondary school compared with the other two groups. Thirty four percent of infants lived with a father who was not in paid employment, with fathers of infants in the control group significantly more likely to be in paid employment than fathers of infants in the MM group.

Sixty three percent of families reported an annual household income of ≤$31,200 and almost one third of the sample (27%) lived in government subsidised housing. A significantly higher proportion of families in the MM group reported receiving a low annual income and living in government subsidised housing compared with families in the control group. While differences between the MM and BM groups on these measures did not reach statistical significance, a greater proportion of families in the MM group reported lower household income and living in government assisted housing. The majority of families (82%) had not moved house in the four months since the birth of the infant enrolled in the study. However 11% (5 controls, 4 BM, 1 MM) had moved house once and six families (7%, 2 BM, 4 MM) had moved house at least twice (range=2-5 times) in the previous four months.

3.6 Maternal psychosocial characteristics at four month follow-up assessment

Information about maternal-infant attachment, postnatal depression, maternal psychological distress, perceived social support and continuing parental substance use was collected at the four month follow up visit.

Maternal postnatal attachment

There were no significant differences between the three groups of women on any of the postnatal attachment subscale scores (Table 3.7). As these scales did not meet the assumptions for parametric statistics and suitable transformations could not be found, differences between groups on each subscale were assessed using Kruskal-Wallis tests.

Median scores for the Quality of Attachment scale (which examines the quality of a mother's emotional response toward her infant) were very similar across the three groups. With a maximum possible score of 45, the majority of women reported a high quality of attachment with their infant (overall median=43.6, range= 31.5-45). With a maximum possible score of 25, median scores for the Absence of Hostility scale were relatively high (overall median= 22, range 12.6-25) indicating that women in the study generally reported high levels of tolerance when interacting with their infant. Median scores for the Pleasure in Interaction scale were very similar across the three groups of women. With a maximum score of 25, the overall median score was high (median=23, range=16-25), indicating that overall women in the study had strong feelings of pride toward their baby, preoccupation with thoughts of the baby during separations, and feelings of joy at reunion with them.

The Global Postnatal Attachment score was significantly negatively skewed and was therefore normalised with a power 5 transformation (i.e. the score multiplied by itself five times) for hypothesis testing. Overall, participants in the study scored relatively highly on the Global Postnatal Attachment score [untransformed $M \pm SD$=86.8±5.7, $F(2,83)$=1.60, p=0.21, range=66.8-95], suggesting that they had strong positive emotions and feelings of attachment toward their infants. The mean global attachment scores observed in this study are slightly higher than those reported by Condon and Corkindale ($M \pm SD$=84.6±7.0, range=59-95) for a community sample of 210 women who completed the Maternal Postnatal Attachment Scale when their infant was four months of age (Condon & Corkindale, 1998). In the current study, women in the MM group had

the highest mean global attachment scores, compared to women in the control and BM groups, although this difference was not statistically significant.

Maternal postnatal depression

The mean Total Score for the Edinburgh Postnatal Depression Scale (EPDS) was moderately positively skewed and was normalised using a square root plus one transformation. The overall mean score for the EPDS in the current study was 7.1 [SD=5.1, $F_{(2,84)}$=0.87, p=0.42, range= 0-21.1], with women in the MM group reporting slightly higher levels of postnatal depressive symptoms than women in either of the other two groups (Table 3.8). While the overall mean is slightly higher than that reported for a sample of over 3000 South Australian women who participated in the *beyondblue* National Postnatal Depression Program ($M\pm SD$=6.2±4.7), the mean EPDS score for the control group in the current study ($M\pm SD$ =6.16±4.6) more closely reflects the South Australian average (Buist & Bilszta, 2005).

The overall incidence of probable minor depression, as defined by an EPDS cut-off score ≥10 (Matthey, et al., 2006), was 26.4%; which is considerably higher than the national Australian average of 15.7% (Buist & Bilszta, 2005). The proportion of women in the current study meeting criteria for probable minor depression is similar to that reported by Edwards et al. (2008) who found that in a sample of 154 South Australian women tested 6 weeks postnatally, 22.6% had a mean EPDS score ≥10. The rate of probable major depression, as defined by an EPDS cut-off score ≥13 (Matthey, et al., 2006), was 17.2%, which is more than twice the national average [7.6%, (Buist & Bilszta, 2005)]. Table 3.8 shows that this observation is driven by the higher levels of symptoms reported by women in the MM group.

Maternal psychological distress

Because the General Health Questionnaire-28 (GHQ-28) total score was significantly positively skewed and a suitable transformation could not be found, Kruskal-Wallis tests were used to

compare the mean ranks of scores between the three groups. There were no significant differences between the three groups of women on the GHQ-28 total score. Neither was there a significant difference in the proportion of women from each group who met criterion for the likelihood of experiencing significant levels psychological distress (score ≥6, Table 3.8). The overall median score of 3 was lower than the recommended criterion score (Goldberg, et al., 1997), with women in the control group reporting the lowest levels of psychological distress and women in the MM group reporting the highest.

Due to the skewness of the data, the statistical significance testing of differences between the groups' _mean_ GHQ-28 scores is problematic. However, in order to provide some comparison with previous research, mean scores will be briefly discussed. Women in the MM group had the highest mean score, which at 6.1 is just above the recommended threshold score of ≥6 (Goldberg, et al., 1997). Women in the BM and control groups had lower mean scores (4.5 and 3.8 respectively) which did not meet the cut-off criterion. The mean scores observed in this study were between three to five times lower than those reported for 127 Norwegian women in a population-based study of post partum depression (Skari, et al., 2002). While the overall mean GHQ-28 total score observed in the current study was 4.7, the mean GHQ-28 total scores in Skari et al.'s study, collected at three time points over the first 6 months post partum, ranged from 22.0 at 0-4 days post partum to 16.7 at 6-months post partum, suggesting that the Norwegian sample had high levels of psychological distress that persisted over time (Skari, et al., 2002). Despite the high mean scores observed in the Norwegian study, the proportion of women who scored above the threshold of ≥6 was lower than in the present sample [21% & 19% (measured at 6 weeks and 6 months post partum) compared with 32% of the current sample].

Perceived social support

In general, the majority of women in the present study reported that they were satisfied with their level of social support. Sixty four percent indicated that the number of people in their day-

to-day life was 'about right'. Generally women in the control group reported greater satisfaction with their level of social support than women in the other two groups. For example, a greater proportion of women in the control group (76%) reported that the number of people in their life was 'about right', compared with women in the BM group (53%) and women in the MM group (58%). Similarly, only 6% of women in the control group indicated that they had no-one to 'lean on', compared with 14% of women in the BM group and 13% of women in the MM group.

Overall, women in the control group scored more highly than women in the other two groups on all four subscales of the Interview Schedule for Social Interaction -Short Form (ISSI-SF), as well as the ISSI-SF Total score (Table 3.9); suggesting they had better perceived availability and adequacy of social integration and attachment. Women in the MM group obtained significantly lower median scores on the Availability of Attachment subscale than women in the control group. Questions in this subscale include 'Do you feel there is one particular person who feels very close to you?' and 'When you are happy is there any particular person you can share it with – someone whom you feel sure will feel happy simply because you are?'. The lower scores obtained by women in the MM group on this subscale indicate a lack of opportunity for developing close relationships.

There was a statistically significant difference in mean ISSI-SF Total scores between women in the MM and control groups with the control group scoring, on average, five points higher than the MM group (Table 3.9). Although the BM group also scored more highly than the MM group, this difference in scores was not significant.

Continuing maternal substance use

At the four month follow-up assessment participating women were asked about their use of substances in the previous month (Table 3.10). Eighty six percent of women in the current study (75/87) reported smoking tobacco in the month prior to the four month follow-up assessment. All

of these women reported smoking daily, with the number of cigarettes smoked per day ranging from 1 to 40. A lower proportion of women in the control group (76%) reported smoking tobacco in the month prior to the follow-up assessment, compared with women in the BM and MM groups (90% & 96% respectively), although this difference was not statistically significant (Fisher's exact test $p=.08$).

Overall, forty women (46%) reported drinking alcohol on at least one occasion in the month prior to the assessment, with a significantly higher proportion of women in the control group reporting alcohol consumption in the past month than women in the other two groups (Table 3.10). The mean number of days that women reportedly consumed alcohol within the month prior to assessment did not differ significantly between groups (4.4±5.7, $F(2,37)=0.83$, $p=.44$, range 1-29 days). Twelve percent of women in the study (10/87) reported use of prescribed psychotropic medication in the month prior to assessment, with a slightly higher proportion of women in the BM and MM groups prescribed a psychotropic medication compared to women in the control group.

Forty eight percent (42/87) of women in the study reported use of an illicit substance in the month prior to the follow-up assessment. A significantly smaller proportion of women in the control group reported use of an illicit substance (21%) compared with both the BM (57%) and MM (75%) groups (Fisher's exact test $p<.001$). All seven women in the control group who reported use of an illicit substance during this time reported use of marijuana only. Five women in the BM group and seven women in the MM reported use of heroin in the previous month, with the majority reporting use on between 1-3 days. One woman in the MM group reported use of heroin on eight days in the previous month while another (also in the MM group) reporting using it on 27 days within the month prior to assessment. Five women in the BM group and four women in the MM group reported use of amphetamines on between 1-12 days in the month prior to the four month follow-up assessment. All of these women reported use of intravenous

methamphetamine or speed. Six women in the BM group and five in the MM group reported use

of a benzodiazepine in the month prior to the follow-up assessment. Women reported use of

Valium®, temazepam or alprazolam on between 1-28 days in last month. All reported taking the

benzodiazepines orally once a day on the days used. It was not reported whether these

substances were prescribed or used recreationally.

3.7 Additional psychosocial factors at 12 and 24 month follow-up assessments

Information about parenting stress and the child's care-giving environment was collected at the

12- and 24-month follow-up visits.

Parenting Stress

At 12 months of age, the overall mean Parent Domain Total Score on the Parenting Stress Index

(PSI) in the current study was 122.98 [SD=25.88, F(2,74)=2.57, p=.08, range= 65-195], with parents

in the BM group reporting slightly higher levels of parenting stress than those in either of the

other two groups (Table 3.11). At 24 months of age, the overall mean Parent Domain Total Score

for the PSI was 124.90 [SD=26.34, F(2,54)=2.38, p=.10, range= 62-205]. Parents in the BM group

again reported higher levels of parenting stress than parents in either of the other two groups

(Table 3.11).The overall mean Parent Domain Total scores at each assessment are lower than that

reported for a sample of 161 women who used opioids and/or cocaine during pregnancy

($M\pm SD$=135.3±17.8), who were assessed when their infant was 18 months of age (Nair, et al.,

2003). However, the mean 24-month PSI Parent Domain score for the BM group in the current

study ($M\pm SD$=136.12±30.20) is similar to that reported by Nair et al. (2003).

Home Environment

The Total Score for the 12-month HOME Inventory was moderately negatively skewed and was

normalised using a square transformation. At 12 months of age, the overall mean Total HOME

Score in the current study was 37.00 [*SD*=3.70, *F*(2,78)=0.22, *p*=80, range= 23.52-42], with all

three groups achieving relatively similar scores (Table 3.11). At 24 months of age, the overall

mean Total HOME Score was 38.01 [*SD*=3.75, *F*(2,64)=4.07, *p*=.02, range= 28.26-45]. Post-hoc

analyses indicated that the mean Total HOME score of the BM group was significantly lower than

that of the MM group (*p*<.05). Mean scores did not differ significantly between the control group

and either of the substance-exposed groups (Table 3.11). Mean HOME scores observed in the

present study were similar to that reported for 180 children randomly selected from the HOME

normative sample (*M±SD*=35.60±6.87) (Boffman, Clark, & Helsel, 1997; Williams et al., 2003).

Total HOME scores were higher than those reported in an American study of infants prenatally

exposed to heroin (*M±SD*=34.0±8.2, *n*=25), methadone (*M±SD*=34.8±6.6, *n*=26), and a non-

exposed comparison group (*M±SD*=32.6±7.9, *n*=41) (Lifschitz, et al., 1985; Wilson, 1989).

CHAPTER 4

Infant Physical Development

This chapter describes the anthropometric data collected at four, 12 and 24 months of age. First, growth measurements (weight, length and HC) were compared across the three groups of infants. Relationships between potential confounding variables and the three growth measures were examined. Differences in growth measurements between groups were then analysed adjusting for significant confounding variables. Finally, changes in growth measurements over time were examined across the three groups of infants.

This chapter addresses the following hypotheses:

Hypothesis 1:

The weight, length and HC of infants prenatally exposed to buprenorphine will not differ significantly from a non-exposed control group when assessed at four, 12 and 24 months of age.

Hypothesis 2:

The weight, length and HC of infants prenatally exposed to methadone will be significantly smaller than those of infants prenatally exposed to buprenorphine and a non-exposed control group of infants when assessed at four, 12 and 24 months of age.

Hypothesis 3:

Change over time in weight, length and HC will not vary significantly between children prenatally exposed to buprenorphine, methadone, or in a non-exposed control group.

Statistical analyses

Prior to analysis the distributions of the dependent variables were assessed for normality and homogeneity of variance between the three groups of infants. A series of simple linear regression analyses (for continuous measures) and ANOVAs (for categorical measures) were conducted to

examine the contribution of potential confounding variables to individual growth measurements at each time point. Each bivariable model was examined for normality and equality of variance and data transformation techniques were employed if these assumptions were not met. Non parametric techniques were used when a suitable transformation was not found. Please refer to the methods section of this thesis (Chapter 2, section 2.7) for a description of the variables chosen for the bivariable analyses.

Standard multiple regression analyses were then conducted to examine the contribution of each independent variable to infant weight, length and HC at each time point, whilst adjusting for the effect of the other variables in the model. Variables were chosen for inclusion in the multivariable models if they were theoretically appropriate and had a significant bivariable relationship with the dependent variable at $p < .05$. Each model was examined for multicollinearity, normality of residuals and equality of variance. Data were transformed using suitable techniques if these assumptions were not met.

A series of split-plot analyses of variance (ANOVAs) were undertaken to examine whether change over time for growth (on each of the three anthropometric measurements) varied between infants in each of the three groups. The between-subjects factors were group (control, BM and MM) and gender (boys and girls). The within-subjects factor was assessment time (four, 12 and 24 months).

4.1 Growth of infants at four months of age

Growth data were collected from 85/87 (98%) infants at four months of age. No growth data were available for two infants in the MM group because their families lived too far away from Adelaide to travel to the WCH for assessment. The 4-month growth data were all positively skewed and did not meet assumptions of constant variance when compared across the groups. Weight at four

months was normalised using an inverse square transformation and a one-way ANOVA was conducted to compare differences in mean weight across the three groups of infants. Kruskal-Wallis tests were used to examine group differences in length and head circumference at four months.

At four months of age, the weight of infants in the control group ranged from 5.17 kg to 9.17 kg, from 5.10 kg to 8.34 kg in the BM group, and from 4.99 kg to 6.89 kg in the MM group. One-way ANOVA showed that, at four months of age, there was a statistically significant difference in the mean weight of infants (Table 4.1) [$F(2,82) = 5.81$, $p<.01$, inverse square transformation]. Bonferroni post hoc analyses showed that infants in the MM group weighed significantly less than infants in both the control and BM groups, while there was no significant difference in weight between the BM and control groups at four months of age. The effect size was moderate at $\eta^2=.12$.

Infants' length at four months of age ranged from 57.4 cm to 68.7 cm for the control group, 57.5 cm to 68.5 cm for the BM group, and 56.3 cm to 63.3 cm for the MM group. A Kruskal-Wallis test, corrected for tied ranks, showed that at four months of age there was a significant difference in length across the three groups of infants [$\chi^2 (2) =8.67$, $n=85$, $p = .01$]. The proportion of variability in the ranked dependent variable accounted for by group was $\eta^2 = .10$, indicating a medium effect of group membership on length at four months of age. Post-hoc Mann-Whitney U tests were conducted to evaluate differences between the three groups. Table 4.1 shows that, at four months of age, the median length of infants in the MM group was significantly shorter than infants in both the control ($z = 2.61$, $p < .01$) and BM groups ($z = 2.60$, $p < .01$). There was no difference in median length at four months of age between infants in the control and BM group ($z = 0.39$, $p =.69$).

Head circumference (HC) at four months of age ranged from 38.5 cm to 44.5 cm for the control group, from 38.0 cm to 44.1 cm for the BM group, and from 39.2 cm to 42.2 cm for the MM group. A Kruskal-Wallis test, corrected for tied ranks, showed that at four months of age there were significant differences between the three groups [χ^2 (2) = 7.83, *n* = 85, *p* = .02]. The proportion of variability in the ranked dependent variable accounted for by group was η^2 = .09, indicating a medium effect of group membership on HC at four months of age. Post-hoc Mann-Whitney U tests were conducted to evaluate differences between the three groups. Table 4.1 shows that, at four months of age, the median HC of infants in the MM group was significantly smaller than infants in the control group (*z* = 2.65, *p* < .01).The median HC of infants in the MM group was slightly smaller than infants in the BM group and this difference had a statistical significance of *p* =.06. There was no difference in median HC at four months of age between infants in the control and BM group (*z* = 1.26, *p* =.21).

4.1.1 Relationship between four month growth measurements and potential confounding variables

Weight at four months of age was significantly associated with birth weight [β = -.55, *t*(82) = -6.03, *p* < .001, inverse square root transformation], gestational age at delivery [β = -.32, *t*(83) = -3.08, *p* < .01, inverse square transformation], and male gender [Kruskal-Wallis: χ^2 (1) = 15.60, *n* = 85, *p*<.001].

Length at four months of age was significantly associated with birth length [β = -.62, *t*(83) = -7.15, *p* < .001, inverse cube transformation], gestational age at delivery [β = .51, *t*(83) = 5.34, *p* < .001, square root transformation], and male gender [*F*(1,83) = 9.69, *p* < .01, inverse transformation].

HC at four months was significantly associated with birth HC [Spearman's rho = .61, n = 85, p <.0001], gestational age at delivery [β = .24, t(83) = 2.21, p = .03], and male gender [F(1,83) = 16.41, *p* < .001, inverse cube transformation].

4.1.2 Four month growth measurements adjusting for potential confounding variables

Variables entered into the first model were 4-month infant weight as the dependent variable (inverse square transformation), with birth weight, gestational age at delivery, infant gender (with girls as the reference), and group (with the control group as the reference) as the predictor variables. The model explained 44% of the variance in weight at four months of age and was significant at $p<.0001$ (Table 4.2). After adjustment for other covariates, birth weight remained a significant predictor of weight at four months of age ($p<.01$) and provided the largest unique contribution to the variance in the model. Male gender also remained a significant predictor of weight at four months of age ($p<.001$) and provided the next largest contribution to the variance in the model. Gestational age at delivery did not provide a significant contribution to the model. Group status was weakly associated with infant weight at four months of age [$F(2,78) = 2.37$, $p = .10$, $\eta^2 = .03$], this was largely due to the difference between the MM group and the BM group [$\beta = .20$, $t(78) = 2.04$, $p = .045$]. At four months of age, weight of infants in the control group did not differ significantly from that of infants in the BM group [$\beta = -.01$, $t(78) = -0.14$, $p = .89$] or the MM group [$\beta = .19$, $t(78) = 1.86$, $p = .07$].

Variables entered into the second model were 4-month infant length as the dependent variable, with birth length, gestational age at delivery, infant gender, and group as the predictor variables. The model explained 50% of the variance in length at four months of age and was significant at $p<.0001$ (Table 4.3). After adjusting for covariates, length at birth remained a significant predictor of length at four months of age ($p<.01$) and provided the largest unique contribution to the variance in the model. Male gender provided the next largest unique contribution to the variance in the model ($p<.001$), while gestational age also continued to be significantly associated with length at four months ($p = .048$). Group status retained a weak association with length at four months of age [$F(2,79) = 2.35$, $p = .10$, $\eta^2 = .03$], largely driven by the difference between the MM group and the BM group [$\beta = -.20$, $t(79) = -2.16$, $p = .03$], with prenatal exposure to methadone remaining a significant predictor of shorter length at four months of age. Four-month length of

infants in the control group did not differ significantly from that of infants in the BM group [β = .07, $t(79)$ = 0.74, p = .46] or the MM group [β = -.14, $t(79)$ = -1.42, p = .16].

Variables entered into the third model were 4-month HC as the dependent variable, with birth HC, gestational age at delivery, gender, and group as the predictor variables. The model explained 47% of the variance in HC at four months of age and was significant at $p<.0001$ (Table 4.4). After adjusting for covariates, HC at birth provided the largest unique contribution to the variance in the model and remained a significant predictor of HC at four months of age ($p<.001$). Male gender provided the next largest unique contribution to the variance in the model and remained significantly associated with HC at four months of age ($p<.01$). Neither gestational age nor group status [$F(2,79)$ = 1.56, p =.22, η^2 = .02] provided significant contributions to the model.

4.1.3 Summary of infant growth at four months of age

Weight   After adjusting for birth weight, gestational age at delivery, and infant gender, weight at four months of age was significantly lower in the MM group compared with the BM group. There was no significant difference in weight at four months of age between the control group and infants in the two substance exposed groups after adjusting for the same covariates, although the difference in weight between the control group infants in the MM group approached statistical significance (p=.07). Birth weight was the strongest predictor of weight at four months of age, and gender remained significantly associated with weight, with boys significantly heavier than girls. Gestational age at delivery did not retain its significant association with weight at four months of age.

Length

After adjusting for birth length, gestational age at delivery, and gender, length at four months of age was significantly lower in the MM group compared with the BM group. There was no difference in infant length at four months of age between the control group and infants in either of the other two groups, after adjusting for the same covariates. Length at birth remained the strongest predictor of length at four months of age, while male gender and older gestational age continued to be significantly associated with greater infant length at four months of age.

Head Circumference

After adjusting for birth HC, gestational age at delivery, and gender, there was no significant difference in HC at four months of age between the three groups of infants. Larger HC at birth and male gender remained significantly associated with larger HC at four months of age. After adjusting for the covariates, gestational age at delivery was no longer a predictor of HC at four months of age.

4.2 Growth of infants at 12 months of age

Growth data were collected from 82/83 (99%) infants at 12 months of age. No growth data were available for one infant in the BM group because he fell asleep before it could be collected. Subsequent attempts to collect this information were unsuccessful. Twelve month length data were unable to be collected from two infants in the BM group because they were unsettled at the time of assessment.

At 12 months of age, the weight of infants in the control group ranged from 8.12 kg to 12.90 kg, from 7.60 kg to 11.85 kg in the BM group, and 6.95 kg to 11.65 kg in the MM group. At 12 months of age, the mean weight of infants in the MM group was almost one kilogram less than infants in the other two groups (Table 4.1). With a moderate effect size of $\eta^2 = .09$, this difference was statistically significant [$F(2,79) = 4.01$, $p = .02$]. Bonferroni post hoc analyses showed that at 12

months of age infants in the control group were significantly heavier than infants in the MM group. Although infants in the BM group weighed slightly more than MM infants at 12 months, this difference was not significant.

Infants' length at 12 months of age ranged from 70.0 cm to 84.0 cm for the control group, 69.5 cm to 82.0 cm for the BM group, and 71.0 cm to 80.0 cm for the MM group. The mean length of infants in the MM group was approximately two centimetres less than infants in the other two groups (Table 4.1). With a moderate effect size of $\eta^2 = .09$, this difference was statistically significant [$F(2,77) = 3.61$, $p = .03$]. Bonferroni post hoc analyses showed that infants in the control group were significantly longer than infants in the MM group. Length at 12 months of age did not differ significantly between the BM and MM groups.

Head circumference at 12 months of age ranged from 43.5 cm to 50.3 cm for the control group, from 44.0 cm to 49.0 cm for the BM group, and from 44.2 cm to 48.2 cm for the MM group. The overall mean HC at 12 months was 46.5 cm (SD=1.41) and none of the group means deviated substantially from this (Table 4.1). Differences in HC between the three groups of infants were not statistically significant [$F(2,97) = 1.25$, p=.29]and the effect size was small (η^2= .03).

4.2.1 Relationship between 12-month growth measures and potential confounding variables
Weight at 12 months of age was significantly associated with birth weight [Spearman's rho=.37, n=81, p<.001] and male gender [$F(1,80) = 11.19$, p <.01]. Length at 12 months of age was significantly associated with birth length [$\beta = .48$, $t(78) = 4.82$, $p < .001$, power .7 transformation], gestational age at delivery [$\beta = .31$, $t(78) = 2.90$, $p < .01$], and male gender [$F(1,78) = 7.51$, p <.01]. HC at 12 months was significantly associated with birth HC [$\beta = .46$, $t(80) = 4.63$, $p < .001$, power .6 transformation], maternal self-reported use of alcohol in pregnancy [$F(1,77) = 4.20$, p <.05], and male gender [$F(1,80) = 17.30$, $p < .001$, log transformation].

4.2.2 Twelve month growth measurements adjusting for potential confounding variables

Variables entered into the first model were 12-month infant weight as the dependent variable, with birth weight, gender (with girls as the reference), and group (with the control group as the reference) as the independent variables. The model explained 27% of the variance in weight at 12 months of age and was significant at *p*<.001 (Table 4.5). After adjusting for group status, gender remained a significant predictor of weight at 12 months of age (*p*<.01) and provided the largest unique contribution to the variance in the model. Birth weight provided the next largest contribution to the variance in the model and was statistically significant at *p*<.05. Group status was not significantly associated with weight at 12 months of age [*F*(2,76) = 1.92, *p* =.15, η^2 = .04], however it is important to note that the difference between the MM group and the control group approached the conventional level of statistical significance [β = -.22, *t*(76) = -1.89, *p* = .06). At 12 months of age, weight of infants in the BM group did not differ significantly from that of infants in the MM group [β = -.18, *t*(76) = -1.55, *p* = .13], or the control group [β = .04, *t*(76) = 0.36, *p* = .72].

Variables entered into the second model were 12-month infant length as the dependent variable, with birth length, gestational age at delivery, gender, and group as the predictor variables. The model explained 32% of the variance in length at 12 months of age (Table 4.6) and was significant at *p* <.0001. After adjusting for covariates, infants' length at birth provided the largest unique contribution to the model and remained significantly associated with 12-month length (*p* <.05). Gender provided the next largest contribution to the model and remained significantly associated with 12-month length at birth (*p*<.01). Gestational age was not significantly associated with length at 12 months, and neither did group status provide a statistically significant contribution to the model [*F*(2,74) = 1.11, *p* = .33, η^2 = .02].

Variables entered into the third model were 12-month infant HC as the dependent variable (square transformation), with birth HC, maternal self-reported use of alcohol in pregnancy (with negative self-report as the reference), gender, and group as the predictor variables. The model

explained 36% of the variance in 12-month HC and was significant at $p<.0001$ (Table 4.7). After adjusting for covariates, birth HC and gender remained significantly associated with 12-month HC, with birth HC providing the largest unique contribution to the model. After adjustment for covariates, maternal self-reported use of alcohol in pregnancy was no longer significantly associated with 12-month HC. As in the univariable analyses, group status was no significantly associated with HC at 12 months of age [$F(2,73) = 0.24$, $p = .79$, $\eta^2 = .004$].

4.2.3 Summary of infant growth at 12 months of age

Weight

After adjusting for birth weight and infant gender, weight at 12 months of age did not differ significantly between the control group and the BM or MM groups, although the difference in 12-month weight between the MM group and the control group did approach statistical significance (p=.06). After adjusting for the same covariates, gender was the strongest predictor of weight at 12 months of age, with boys significantly heavier than girls. Birth weight also remained significantly associated with weight at 12 months of age.

Length

After adjusting for birth length, gestational age at delivery, and gender, infant length at 12 months of age did not differ significantly between the three groups of infants. Birth length was the strongest predictor of length at 12 months of age after adjusting for the same covariates, and gender remained significantly associated with infant length, with boys significantly taller than girls. Gestational age was not significantly associated with length at 12 months.

4.3 Growth of infants at 24 months of age

Growth data were collected from 73/73 (100%) infants at 24 months of age. Twenty four month

length data were not collected from two infants in the MM group who were unsettled at the time

of assessment. Twenty four month HC data were not available for seven infants (1 control, 1 BM,

5 MM), six of whom were unsettled and one because of a data measurement error (this infant's

HC was recorded as 18 cm which was clearly a measurement error). Length at 24 months of age

was positively skewed and was normalised using an inverse cube transformation. Head

circumference at 24 months of age did not meet the assumption of homogeneity of variance and

a suitable transformation could not be found. Kruskal-Wallis tests were therefore used to describe

differences between the three groups on this measure.

At 24 months of age, the weight of infants in the control group ranged from 10.90 kg to 16.60 kg,

from 10.20 kg to 15.30 kg in the BM group, and 9.80 kg to 14.20 kg in the MM group. One-way

ANOVA showed that, at 24 months of age, there was a statistically significant difference in the

mean weight of infants (Table 4.1) [$F(2,70) = 4.10$, $p <.05$]. The effect size was moderate at $\eta^2 =$

.10. Bonferroni post hoc analyses revealed that infants in the MM group weighed significantly less

than infants in the control group ($p = .02$), but the difference between the BM and MM groups did

not reach statistical significance. Neither was there a significant difference in weight between the

BM and control groups at 24 months of age.

Infants' length at 24 months of age ranged from 81.3 cm to 97.5 cm for the control group, 80.5 cm to 95.0 cm for the BM group, and 78.5 cm to 88.7 cm for the MM group. One-way ANOVA showed that there was no significant difference between the three groups of infants in terms of length at 24 months of age (Table 4.1) [$F(2,68)$ = 1.96, p = .15, inverse cube transformation].

Head circumference (HC) at 24 months of age ranged from 45.00 cm to 52.00 cm for the control group, from 46.5 cm to 50.5 cm for the BM group, and from 46.90 cm to 49.30 cm for the MM group. A Kruskal-Wallis test, corrected for tied ranks, showed that at 24 months of age there was a significant difference in median HC across the three groups [χ^2 (2) = 7.49, n= 66, p = .02]. The proportion of variability in the ranked dependent variable accounted for by group was η^2 = .12, indicating a medium effect of group membership on HC at 24 months of age. Post-hoc Mann-Whitney U tests were conducted to evaluate differences between the three groups. Table 4.1 shows that, at 24 months of age, the median HC of infants in the MM group was significantly smaller than infants in the control group (z = 2.45, p = .014). There was no significant difference in median HC at 24 months of age between infants in the BM and MM groups (z = 1.27, p = .20). The median HC of infants in the BM group was slightly smaller than infants in the control group although this difference did not reach statistical significance (z = 1.91, p = .06).

4.3.1 Relationship between 24-month growth measures and potential confounding variables
Weight at 24 months of age was significantly associated with birth weight [Spearman's rho= .36, n=72, p<.01], and male gender [$F(1,71)$ = 17.03, p < .001]. Length at 24 months of age was significantly associated with birth length [β = .42, $t(69)$ = 3.84, p < .001] and male gender [Kruskal-Wallis: χ^2 (1) = 10.03, n= 71, p<.01]. HC at 24 months was significantly associated with birth HC [β = .41, $t(64)$ = 3.63, p < .001, log transformation], and male gender [$F(1,64)$ = 24.48, p < .001].

4.3.2 Twenty four month growth measurements adjusting for potential confounding variables

Variables entered into the first model were 24-month weight as the dependent variable (power 5 transformation), with birth weight, gender (with girls as the reference), and group (with the control group as the reference) as the predictor variables. The model explained 35% of the variance in weight at 24 months of age and was significant at $p<.0001$ (Table 4.8). After adjusting for group status, gender remained a significant predictor of weight at 24 months of age ($p<.001$) and provided the largest unique contribution to the variance in the model. Birth weight provided the next largest contribution to the variance in the model and was statistically significant at $p<.05$. Group status was weakly associated with 24-month weight [$F(2,67) = 2.27$, $p = .11$, $\eta^2 = .04$], largely due to the difference between the MM group and the control group [$\beta = -.24$, $t(67) = -2.10$, $p = .04$]. At 24 months of age, the weight of infants in the BM group did not differ significantly to that of infants in the MM group [$\beta = -.18$, $t(67) = -1.52$, $p = .13$], or the control group [$\beta = .07$, $t(67) = 0.62$, $p = .54$].

Variables entered into the second model were 24-month length as the dependent variable, with birth length, infant gender (with girls as the reference) and group (with the control group as the reference) as the predictor variables. The model explained 33% of the variance in length at 24 months of age (Table 4.9) and was significant at $p <.0001$. After adjusting for covariates, male gender provided the largest unique contribution to the model and remained significantly associated with 24-month length ($p <.001$). Length at birth provided the next largest contribution to the model and remained significantly associated with 24-month length at birth ($p<.01$). Group status was not significantly associated with length at 24 months of age [$F(2,66) = 0.75$, $p = .48$, $\eta^2 = .02$].

Variables entered into the third model were 24-month HC as the dependent variable, with birth HC, infant gender (with girls as the reference), and group (with the control group as the reference), as the predictor variables. The model explained 43% of the variance in 24-month HC

and was significant at p <.0001 (Table 4.10). After adjusting for covariates, male gender and HC at birth remained significantly associated with 24-month HC, with gender providing the largest unique contribution to the model. After adjustment for covariates, group status was not significantly associated with HC at 24 months of age [F(2,61) = 2.04, p = .14, η^2 = .04], however the difference between the MM group and the control group approached statistical significance [β = -.20, t(61) = -1.85, p = .07]. At 24 months of age, HC of infants in the BM group did not differ significantly from that of infants in the MM group [β = -.07, t(61) = -0.61, p=.54], or the control group [β = .16, t(61) = 1.48, p = .14].

4.3.3 Summary of infant growth at 24 months of age

Weight

After adjusting for birth weight and gender, weight at 24 months of age was significantly lower in the MM group when compared with infants in the control group. Weight at 24-months did not differ significantly between infants in the control group and the BM group, or between the two maintenance exposed groups of infants. Gender was the strongest predictor of weight at 24 months of age, with boys significantly heavier than girls. Birth weight also remained significantly associated with weight at 24 months of age.

Length

After adjusting for birth length and gender, length at 24 months of age did not differ significantly between the three groups of infants. Gender was the strongest predictor of length at 24 months of age, with boys significantly longer than girls, and length at birth continued to be significantly associated with 24-month length.

Head Circumference

After adjustments for birth HC and gender, HC at 24 months of age did not differ significantly between the three groups of infants, although the difference between the MM and the control group did approach statistical significance (p=.07). After adjusting for covariates, gender was the strongest predictor of HC at 24 months of age, with boys having significantly larger HC than girls. HC at birth also remained significantly associated with 24-month HC.

4.4 Longitudinal analyses of growth measurements

Figures 4.1 to 4.3 show the mean growth measurements of each group over the three follow-up assessments. A series of split-plot analyses of variance (ANOVA) were undertaken to examine whether change in growth (means for each of the three anthropomorphic measures) over time varied between each of the three groups. The between-subjects factors were group (control, BM and MM) and gender (boys and girls). The within-subjects factor was time (4-, 12- and 24-months). The corresponding birth measurement, treated as a within-subjects factor, was entered as a covariate for each model. Preliminary checks were conducted to ensure that there was no violation of the assumptions of normality, linearity, homogeneity of variances, and homogeneity of regression slopes.

Weight

As expected, after adjusting for birth weight, the ANOVA showed that there was a statistically significant main effect for time [$F_{(2,145)}$ = 1649.88, p <.0001, η^2 = .70]. There was no significant main effect of gender [$F_{(1,81)}$ = 1.57, p= .21, η^2 = .002]. Neither was there a significant main effect of group [$F_{(2,81)}$ = 1.80, p = .17, η^2 = .004] or birth weight [$F_{(1,81)}$ = 2.82, p = .10, η^2 = .003]. The time × group interaction did not reach statistical significance [$F_{(4,145)}$ = 1.38, p = .25, η^2 = .001], suggesting that change in mean weight over time did not vary significantly between the three groups of infants. The weak association between group status and weight noted in the individual cross-sectional analyses became weaker still in the overall longitudinal analysis.

Length

After adjusting for length at birth, the ANOVA showed that there was a significant main effect for time [$F(2,143)$ = 3336.20, p <.0001] with a large effect size (η^2 = .78), indicating that, as expected, overall mean length significantly increased over the follow-up assessments. There was also a significant main effect of birth length [$F(1,82)$ = 4.96, p = .03], although this effect was very small (η^2 = .002). There was no significant main effect of gender [$F(1,82)$ = 1.07, p = .30, η^2 = .0005] or group [$F(2,82)$ = 1.01, p = .37, η^2 = .001]. The time × group interaction was not significant [$F(4,143)$ = 0.12, p = .97, η^2 = .00006], indicating that change in mean length over time did not vary significantly between the three groups of infants.

Head Circumference

After adjusting for HC at birth, the ANOVA showed that there was a strong main effect for time [$F(2,140)$ = 2505.69, p <.0001, η^2 = .70], indicating that, as expected, overall HC increased significantly over the three follow-up assessments. There was no significant main effect of birth HC [$F(1,82)$ = 1.09, p = .30, η^2 = .001], gender [$F(1,82)$ = 0.75, p = .39, η^2 = .0007] or group [$F(2,82)$ = 0.34, p = .71, η^2 = .0006]. The time × group interaction was not significant [$F(4,140)$ = 0.65, p = .63, η^2 = .0004], showing that change in mean HC over time did not vary significantly between the three groups of infants.

4.4.1 Summary of growth longitudinal analyses

Results of the three split-plot ANOVAs showed that change in anthropometric mean data over the three follow-up assessments did not differ significantly between infants prenatally exposed to buprenorphine, methadone or the non-exposed control group of infants. None of the interactions between group status and time were significant, indicating that change in growth measurements over the three follow-up assessments did not differ significantly between the three groups of infants.

4.5 Discussion

This chapter compared the physical development of infants exposed to buprenorphine or methadone in pregnancy with that of a group of non-exposed infants. The key finding was that the physical development of infants prenatally exposed to buprenorphine did not differ significantly from that of a group of non-exposed infants in terms of their weight, length or HC at four, 12 or 24 months of age. There was no change in this relationship after adjustment for covariates, including birth measurements and gender. This is an important finding in terms of providing support for the ongoing use of buprenorphine in pregnancy. At four months of age, weight of infants prenatally exposed to methadone remained significantly lower than buprenorphine-exposed infants, after adjusting for covariates. Weight did not differ between the three groups at 12 months in multivariable analyses, although the cross-sectional analyses at 24 months of age found that infants prenatally exposed to methadone were significantly lighter than non-exposed control infants, after adjusting for birth weight and gender. At four months of age, length remained significantly lower in the MM group compared with the BM group, after adjusting for birth length, gestational age at delivery, and gender. After adjusting for covariates, no differences were observed for infant length at 12 or 24 months of age. Head circumference did not differ significantly between the three groups of infants at any of the three assessments after adjusting for covariates. This is a reassuring finding in regards to use of both buprenorphine and methadone during pregnancy, as HC is an important indicator of brain growth and subsequent cognitive development (García-Alix, Sáenz-de Pipaón, Martínez, Salas-Hernández, & Quero, 2004; Noyola et al., 2001). Weight, length and HC at birth, and male gender remained the strongest predictors of having larger anthropometric measurements at four, 12 and 24 months of age. Whilst some of these cross-sectional findings are not entirely consistent with the longitudinal findings, it is important to bear in mind that there were fewer subjects with complete data for all three assessments than for the individual cross-sectional analyses, and subject numbers available at each assessment may be critical in a study of limited power. As hypothesised, change in anthropometric measures over time did not vary significantly between the three groups of

infants. This was expected as only one study has reported a change in infant length over time for methadone-exposed infants compared with non-exposed controls (Hunt, et al., 2008). Whilst the authors of this study reportedly adjusted analyses for maternal height, maternal smoking and gestation, no other covariates were discussed and no explanations for the obtained results were provided.

The opioid system plays an important role in growth and development, and opioid receptors are found in the brain, spinal cord, and other organ sites in the developing foetus (Farid, et al., 2008; Jaffe, et al., 1997). Opioid receptor expression is regulated by signals from growth factors and neurotransmitters, both of which are affected by prenatal exposure to opioids (Robinson, 2000, 2002; Tiong & Olley, 1988; Wu, et al., 2001). An example of this is the zeta (ζ) opioid growth factor receptor which is found throughout the developing rat brain, but is not present in the brains of adult rats. The ζ-receptor, which is involved with the mediation of foetal cell proliferation, is regulated by the endogenous ligand [Met5]-enkephalin, also known as opioid growth factor. It is thought that prenatal exposure to opioid agonists, such as methadone or heroin, may affect foetal developmental processes by interacting with the ζ-receptor to impede normal growth. Conversely, prenatal exposure to opioid antagonists (BM has some antagonist effects) may prevent [Met5]-enkephalin from binding with the ζ-receptor, thus blocking the growth-inhibitory response (Farid, et al., 2008). Early research has shown that rat pups prenatally exposed to high-dose (8 mg/kg/day) methadone showed significant decreases in Met- and Leu-enkephalin levels in the striatum, compared with pups prenatally exposed to low-dose (4 mg/kg/day) methadone, or high- and low-dose (1 or 2 mg/kg/day) buprenorphine (Tiong & Olley, 1988). [Met5]-enkephalin is expressed in both neural (i.e. cerebrum and cerebellum) and somatic (i.e. bone and muscle) areas of the developing foetus. Suppression of cell viability in these regions is thought to be associated with smaller size and weight in opioid-exposed newborns (Farid, et al., 2008; Herlenius & Lagercrantz, 2004).

Studies have also shown that prenatal exposure to opioids may affect the production of the hormones in the endocrine system responsible for foetal growth and development. The hypothalamic-pituitary-adrenal (HPA) axis is a feedback loop encompassing the release of corticotrophin-releasing hormone (CRH) from the hypothalamus, which stimulates the release of adrenocorticotropin (ACTH) from the pituitary gland, and in turn the release of the adrenal cortical hormones, corticosterone and cortisol (the primary glucocorticoid involved in the stress response in humans). The release of adrenal cortical hormones completes the feedback loop as it has a negative feedback effect on the hypothalamus and pituitary gland (Konijnenberg & Melinder, 2011). Prenatal exposure to opioids may disrupt normal foetal endocrine function either via direct exposure of the foetus to opioids, or indirectly through changes in maternal endocrine functioning. During pregnancy there is a positive feedback loop between CRH in the placenta and maternal adrenal cortisol. While levels of CRH and cortisol increase as the pregnancy progresses, only 10 to 20% of maternal cortisol reaches the developing foetus as it is converted to the inactive form cortisone by an enzyme in the placenta. In the developing foetus, CRH has a pivotal role in foetal growth and maturation, as well as influencing the onset of parturition (Ellman et al., 2008; Konijnenberg & Melinder, 2011). Exposure to cortisol during the final trimester of pregnancy is vital for the development of numerous physiological systems and for overall foetal growth. However, it has been shown that prenatal exposure to synthetic corticosterioids may be associated with intrauterine growth restriction and low birth weight, and that maternal and placental levels of CRH may also influence foetal growth and gestational length (Ellman, et al., 2008). Ellman and colleagues (2008) found that foetal exposure to elevated levels of maternal plasma cortisol early in pregnancy, and placental CRH in late pregnancy was significantly associated with decreased newborn physical and neuromuscular maturation, independent of gestation.

Opioid agonists, such as morphine and methadone, are known to inhibit the HPA-axis in adult humans by decreasing levels of plasma cortisol, and antagonists, such as naloxone, are known to

stimulate the HPA-axis, subsequently increasing plasma levels of both ACTH and cortisol. The opposite effect is seen in animal models whereby opioid agonists stimulate, and opioid antagonists inhibit, the HPA-axis (Pechnick, 1993). Animal studies have indicated that acute administration of morphine stimulates the release of adrenal cortical hormones and ACTH, whilst buprenorphine (also administered acutely) does not have a stimulatory effect on the HPA-axis (Gomez-Flores & Weber, 2000; Konijnenberg & Melinder, 2011; Pechnick, 1993). Buprenorphine's partial agonist properties have been hypothesised to be responsible for its differing effect on endocrine functioning compared with full agonists such as morphine (Gomez-Flores & Weber, 2000). Additionally, it has been suggested that exposure to opioids could alter the hypothalamic CRH content and influence the release of CRH from the hypothalamus (Pechnick, 1993). Thus maternal use of opioids during pregnancy may negatively affect infant growth and development via alterations in hormone levels within the maternal endocrine system.

The findings of the present study suggest that prenatal exposure to methadone may have a pervasive influence on physical development, particularly in terms of infant weight, over and above environmental factors. Whilst gender and birth measurements were the strongest predictors of physical development for each of the three measures at all follow-up assessments, prenatal exposure to methadone continued to have an association with lower weight, particularly in comparison to the non-exposed group of infants. When the effect of covariates (including birth weight) was included in analyses, differences in weight between the MM and control groups did not reach conventional levels of statistical significance at four or 12 months of age. However, these differences may have been significant, by conventional criteria, if the sample size had been larger.

Specifically considering buprenorphine, it is pertinent to note that weight and length at four months of age continued to be significantly higher in the buprenorphine-exposed group,

compared with the methadone-exposed infants, after adjusting for covariates. This finding may contribute support to the use of buprenorphine as an opioid-maintenance option in pregnancy.

The finding in the present study that infants in the MM group continued to have lower weight than a non-exposed group of infants, until at least two years of age, is consistent with research by van Baar et al. (1994), who reported that growth restrictions were apparent until early childhood for a group of children prenatally exposed to opioids, when compared with a non-exposed control group. Similarly, Soepatmi (1994) found that infants prenatally exposed to opioids (methadone and heroin) had significantly smaller growth percentiles for weight, length and HC at two years of age, than children in the general Dutch population. Consistent with the theory that opiate-induced growth restrictions often decrease over time (Farid, et al., 2008), Soepatmi reported that at follow-up, when the children were aged between 3.5 and 12 years of age, growth percentiles for weight and HC had caught up to the Dutch norms, although growth percentiles for length remained significantly lower (Soepatmi, 1994).

The results of the present study differ from previous research which has shown that infants prenatally exposed to methadone experience a 'catch up' effect, over time in weight, but a tendency for continued shorter length or smaller HC, compared with non-exposed infants (Hans, 1989; Hunt, et al., 2008; H. L. Johnson, et al., 1987, 1990; Rosen & Johnson, 1982). Hunt et al. (2008) reported no differences in unadjusted weight or HC at 18 months and three years of age between infants prenatally exposed to methadone and a non-exposed control group. However, after adjusting for gestational age at delivery, maternal height and maternal smoking, infants in the MM group remained significantly shorter than the non-exposed infants at both of these assessments (Hunt, et al., 2008). Johnson and colleagues reported that weight and height did not differ at 36 months of age between methadone-exposed and non-exposed infants; however it was reported that a significantly greater proportion of children exposed to methadone had HC measurements below the third percentile at this assessment, when compared with the non-

exposed group (H. L. Johnson, et al., 1987, 1990). Hans reported smaller HC and shorter length, for methadone-exposed infants at two years of age, compared with non-exposed infants (Hans, 1989).

It is difficult to ascertain what may be the cause of the weight 'catch up' effect observed in the above mentioned studies, as most of the publications did not provide sufficient information with which to make sound conclusions. However, research has indicated that higher doses of maternal methadone maintenance in humans (i.e. >40mg/day) may be associated with greater suppressant effect on infant growth (Farid, et al., 2008). The mean methadone dose in Hans' (1989) study was reportedly less than 20 mg/ day, while the mean maternal dose of methadone in pregnancy for the current study was 45.41±20.21 mg/ day (range 15-100 mg). It is feasible that maternal dose may have contributed to the continued lower weight for methadone-exposed infants in the current study. Although, if this is the case, it would perhaps be expected that length and HC would have also continued to be smaller in this group, which was not evident in the present study. Mean maternal methadone dose in the Rosen/Johnson cohort (H. L. Johnson, et al., 1987, 1990; Rosen & Johnson, 1982) was similar to the present study at 42.9±2.6 mg/ day, suggesting that maternal dose may not be responsible for the catch up effect, or that unmeasured sample characteristics may have influenced infant growth. Rosen and Johnson (1982) suggested that deficits in the CNS may be associated with small HC, and smaller HC has been observed in poly-substance exposed children compared with non-exposed controls at three years of age (Azuma & Chasnoff, 1993). Infants in the Rosen/Johnson (H. L. Johnson, et al., 1987, 1990; Rosen & Johnson, 1982) research were prenatally exposed to substances other than methadone which may have independently negatively affected brain growth and development. Similarly, Hans' (1989) sample were exposed to other substances *in utero*. Neither study adjusted for other substance exposure in analyses of infant growth.

Research comparing the neonatal growth of infants prenatally exposed buprenorphine and methadone has found only modest differences in birth measurements. Jones and colleagues (2005) found that infants prenatally exposed to buprenorphine were an average of 528 gm heavier at birth than infants prenatally exposed to methadone, although this difference did not reach conventional levels of statistical significance (p=.09), the study sample being very small (N=20). Other studies have reported no differences in birth measurements (Ebner, et al., 2007; Fischer, et al., 2006; Jones, et al., 2010; Kakko, et al., 2008; Lejeune, et al., 2006).

There is limited published research on the development of infants prenatally exposed to buprenorphine beyond the neonatal period, and the current study appears to be the most comprehensive documentation of the physical growth of these infants. Previous studies describing development of infants exposed to buprenorphine *in utero* have reported growth outcomes within normal limits (Kayemba-Kay's & Laclyde, 2003; Sandtorv, et al., 2009; Schindler, et al., 2003). Two of the publications (Kayemba-Kay's & Laclyde, 2003; Schindler, et al., 2003) were case-note review studies and follow-up growth data were not reported. The only study to include both methadone- and buprenorphine-exposed infants did not provide long term growth data and did not report growth outcomes separately for the two groups of infants (Sandtorv, et al., 2009). All studies were limited by low subject numbers (N = 4 to 15).

Animal studies have also shown mixed results, with Tiong et al. (1988) reporting that rat pups prenatally exposed to 1 mg or 2 mg /kg /day buprenorphine, weighed less than pups exposed to 4 mg or 8 mg/kg/day methadone and non-exposed control pups, on postnatal day 20. The authors reported that pup mortality (by postnatal day 5) was significantly greater in the buprenorphine-exposed groups. This was attributed to either rejection by non-treated foster mothers or pup viability, with the authors suggesting that the causes be further investigated (Tiong & Olley, 1988). Lichtblau and Sparber (1981) have suggested that pup-mortality may be associated with neonatal withdrawal. However this was not measured in Tiong and Olley's publication (1988). Additionally,

it has been suggested that persistent opioid-agonist activity in the developing brain may suppress feeding and other behaviours required for normal growth and survival (Lichtblau & Sparber, 1981).

Hutchings et al. (1992) found that higher maternal doses of methadone had a transient effect on the postnatal growth of rat pups, with pups prenatally exposed to higher doses of methadone showing initial deficits in weight gain, compared with pups prenatally exposed to lower-dose methadone and a non-treated control group. The authors reported a catch-up in weight by the 50th postnatal day for the pups exposed to high-dose methadone, but suggested that the delay in growth could have been secondary to NAS symptoms (Hutchings, et al., 1992). Further research by this group found no differences in birth weight or postnatal growth (to postnatal day 60) between rat pups prenatally exposed to differing amounts of buprenorphine, and pups in a non-exposed control group (Hutchings, et al., 1995).

In summary, and to put the results of the current study in the context of previous research, there are four key explanations for the differences in growth observed. As described above, the lower weight and smaller stature of the MM-exposed infants may be due to the interaction of methadone with the endogenous ligand [Met5]-enkephalin in the developing foetus. This may have the effect of inhibiting cell proliferation in the brain, along with somatic structures including muscle and bone. Conversely, the antagonist effects of buprenorphine may be responsible for blocking this growth-inhibitory response, thus resulting in growth acceleration in buprenorphine-exposed infants (Farid, et al., 2008).

A second explanation for the observed differences in growth outcomes for methadone- and buprenorphine-exposed infants may be the differing effects of the two drugs on maternal or infant endocrine functioning. As described above, it is possible that methadone may negatively influence the HPA-axis to increase maternal and placental CRH and ACTH levels, which in turn may

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inhibit foetal growth. Due to its partial agonist properties, buprenorphine may not have the same influence over endocrine functioning (Gomez-Flores & Weber, 2000; Konijnenberg & Melinder, 2011; Pechnick, 1993).

A third reason for the differences in growth for BM and MM exposed infants in the present study may be higher maternal doses of methadone during pregnancy contributing to suppression of foetal growth (Farid, et al., 2008; Hutchings, et al., 1992). The mean maternal dose for women in the present study (45.41±20.21 mg/day) may, in part, explain why infants in the MM group experienced delays in growth, particularly in relation to weight gain. The mean buprenorphine dose in the current study was 7.33±4.29 mg (range 0.4-20 mg), and while it has been demonstrated that 8 mg BM is comparable to 60 mg MM (Farid, et al., 2008; Ling & Wesson, 2003) in terms of effectively treating heroin use and dependence, the finding that infants in the BM group did not differ in their postnatal growth from a group of non-exposed infants is analogous to that of Hutchings et al. (1995), as outlined above.

Finally, the observed differences in growth outcomes observed in the present study may be associated with the differing placental transfer of the two drugs. In vitro models have shown that whilst both substances are sequestered in human placental tissue, the concentration ratio of buprenorphine in the tissue/foetal circuits (27.4 ± 0.4) is higher than that of methadone (9.9 ± 1.2), indicating that a greater proportion of buprenorphine is retained in maternal tissue, comparative to methadone (Nanovskaya, et al., 2002; Nekhayeva, et al., 2005). Additionally, whilst both substances cross the placenta from mother to foetus, the maternal to foetal transfer is greater for methadone (29.4±4.6%) than for buprenorphine (11.6±2.5%) (Nekhayeva, et al., 2005). The lower concentration of buprenorphine in the foetal circulation, which has been associated with reduced incidence and severity of NAS, compared with methadone, may also influence differences in physical growth in BM and MM exposed infants (Nanovskaya, et al., 2002). In addition, infants with severe NAS symptoms may experience difficulty with feeding and

show increased energy expenditure, both of which may contribute to deficits in growth in MM-exposed infants (Hutchings, et al., 1992).

It is unlikely that postnatal factors contributed to the continued lower weight of the MM group in the current study. Groups were comparable on a range of factors which may influence infant growth (see Chapter 3), and analyses were adjusted for socio-demographic factors that differed between groups. The MM infants may have had more difficult temperaments, compared with the BM and control groups, and could have been fussier eaters. However, as shown in Chapter 7, parent-rated Temperament did not differ between the three groups of infants. Thus, it is unlikely that poorer food intake or diet quality were confounding factors in terms of infant growth in the current study.

CHAPTER 5

Infant Visual Evoked Potentials

This chapter describes the visual evoked potential (VEP) latencies of infants at four months of age.

First, mean latencies to the first major positive peak (P1) of the neuronal response to two

different sized stimuli (48' and 69' of retinal arc – see footnote in Chapter 2, for a definition) were

evaluated for each of the three groups of infants. Second, relationships between potential

confounding variables and VEP latencies were examined, and differences in latencies between

groups were then adjusted for confounding variables.

This chapter has previously been published in a peer-reviewed journal (see Statement of

Authorship). As the sample size in the manuscript differs from the thesis sample, the demographic

detail described in this chapter differs from that presented in Chapter 3 (see section 5.1 below).

VEP data from a subset of the current study sample was analysed for my Master of Clinical

Psychology thesis, however the analyses utilised and the content of this chapter are substantially

different from the Master's thesis (see Appendix O for note regarding the content of this chapter).

The present chapter addresses the following hypotheses:

Hypothesis 4: Infants prenatally exposed to buprenorphine will have significantly shorter P1

latencies at four months of age, suggesting greater visual maturation, than children prenatally

exposed to methadone.

Hypothesis 5: The P1 latencies of infants prenatally exposed to buprenorphine will not differ

significantly from those of a non-exposed control group, when measured at four months of age.

Statistical analyses

One-way ANOVA were conducted to test the statistical significance of differences between the mean latencies of the P1 response to each check size across the three groups. Post hoc tests using the Bonferroni procedure were employed to identify the statistical significance of differences between pairs of groups. Because a number of factors may contribute to differences in VEP outcome (Khedr, et al., 2004; Makrides, Neumann, Jeffrey, Lien, & Gibson, 2000), one-way ANOVA with Bonferroni adjustments were also conducted to test for differences between the mean scores of each group for continuous covariates (one and five minute APGAR scores, gestational age, weight, length and HC at birth, child's age at testing, child's corrected age at testing, mother's age). Chi square analyses and Fisher's exact tests were used to examine the differences among the three groups for categorical variables (prenatal exposure to other substances, child's gender, breastfeeding status, whether the child received pharmacological treatment for NAS, parents' educational level, fathers' employment status, family structure, household income, accommodation). Pearson product-moment correlation coefficients revealed no significant relationship between average antenatal maternal maintenance dose and P1 latency for either of the drug-exposed groups (BM: 48' r= -.27, n=29, p=.15; 69' r= -.10, n=29, p=.59; MM: 48' r= -.03, n=20, p=.90; 69' r= .33, n=22, p=.13). Subsequently, standard multiple regression analyses were conducted to adjust for the effects of potentially confounding variables on the relationship between group status and P1 latency. Variables were chosen for inclusion in the multivariable analyses if they were significantly different between groups (Table 5.1).

5.1 Latency of Visual Evoked Potentials at four months of age

VEP latency data were collected from 98% (85/87) of participating infants. Two infants in the MM group (both male) lived too far away for the families to travel to the Women's and Children's Hospital (WCH) for VEP testing and their demographic data are not included in analyses for this chapter. Responses to the smaller (48 min of arc) stimulus were successfully collected from 83/85

infants (98%). One infant was too tired and distressed to complete the assessment for the smaller

stimulus, while the P1 latency response for the second infant to this stimulus was not detectable.

Both of these infants were female and in the MM group. Responses to the larger (69 min arc)

stimulus were available from all 85 infants and were used in analyses.

Sensitivity analyses

Because measureable responses to smaller stimuli may not be evident in very young infants, and

as VEP outcome may be influenced by environmental factors, latencies were collected at four

months chronological age (Khedr, et al., 2004; Makrides, Neumann, & Gibson, 2001; Moskowitz &

Sokol, 1983). Parents were invited to attend an appointment at the Women's and Children's

Hospital at ± 1 week of their infant reaching four months (chronological) age. However, because

not all families were available at this time, infants' chronological age at testing ranged from 13.00

to 31.40 weeks (*M*=17.24, *SD*=2.45). To adjust for delays in neuronal development attributable to

either testing age or gestational age, a corrected age variable (corrected age = chronological

weeks of age at VEP testing + gestational age at birth - 40 weeks) was calculated. Corrected age

did not differ significantly between the three groups of infants [overall *M*=15.85 weeks, *SD*=3.11,

$F(2,82)=2.35$, *p*=0.10].

One-way ANOVA were conducted to test whether mean latencies of the P1 response to each VEP

check size differed between the groups tested on the two different VEP systems. There was no

significant difference in P1 latencies for checks of 48' [$F(1,81)=0.11$, *p*=0.74] for children assessed

using the different VEP equipment; however there was a significant difference for checks of 69'

[$F(1,83)=4.48$, *p*=.04]. There was no significant difference between the three groups in terms of

the percentage of infants assessed on the two VEP systems (Fisher's exact test *p*=.17). In order to

retain statistical power, subsequent analyses combined data from both VEP systems but

equipment was included as a covariate in the multivariable analyses.

Exposure to phenobarbitone has been shown to produce changes in the neonatal brain (Holmes, Harden, Liporace, & Gordon, 2007; Stefovska et al., 2008) and to have an effect on later visual development (Brinciotti, 1994) and long-term cognition (Meador, Baker, Cohen, Gaily, & Westerveld, 2007). Sensitivity analyses were conducted to test whether inclusion of the three infants treated with phenobarbitone contributed to differences in VEP latencies between infants treated pharmacologically for neonatal abstinence syndrome (NAS) versus those not treated. One-way between-groups ANOVA excluding the three infants treated with phenobarbitone showed no significant difference in mean latencies between infants treated with morphine versus infants not pharmacologically treated for NAS (48': [$F(1,45)=0.00$, $p=0.95$]; 69': [$F(1,47)=0.55$, $p=0.46$]). When the infants treated with phenobarbitone were included in the analyses, results remained non significant (48': [$F(1,48)=0.22$, $p=0.64$]; 69': [$F(1,50)=0.29$, $p=0.59$]). Thus data from all infants were included in the final analyses.

Two infants in the MM group had considerably longer P1 latencies than the other infants in response to one or both check sizes. Because the unadjusted VEP data were not normally distributed, the analyses were conducted in three ways: 1) without adjusting the data, 2) after first removing the data from the two outlying MM infants, and 3) using an inverse square transformation including data for all participating infants. Sensitivity analysis revealed significant differences in P1 latency for both check sizes when all participants were included in the unadjusted analyses. When the data from the two MM outliers was removed the significance of the differences between the groups was reduced, however the MM group continued to have longer latencies in response to both check sizes. The effect sizes (calculated using eta squared) were .07 and .04 for 48' and 69' checks respectively. When data from all participants were adjusted using an inverse square transformation, significant differences in P1 latency remained. As there was no reason to exclude the two MM infants on medical or equipment grounds, and

because there were already smaller numbers in the MM group, the transformed data with all participants included were used in the final analyses.

VEP latencies

Table 5.2 shows that there was a statistically significant difference in P1 latencies in response to checks of 48' between the three groups of infants [$F(2,80)=5.05$, $p<.01$, inverse square transformation]. The effect size was moderate at $\eta^2=.10$ (Cohen, 1988). Post hoc comparisons indicated that P1 latencies in response to checks of 48' for infants exposed to methadone were significantly longer than those of both control infants ($p<.05$) and infants exposed to buprenorphine ($p<.05$). There was no significant difference in P1 latencies in response to checks of 48' between buprenorphine-exposed infants and control infants ($p=1.0$). In addition, there was a statistically significant difference between P1 latencies in response to checks of 69' across the three groups [$F(2,82)=3.93$, $p<.05$, inverse square transformation], with a moderate effect size of $\eta^2=.09$. Post hoc comparisons showed that P1 latencies in response to checks of 69' for infants exposed to methadone were significantly longer than those of both control infants ($p<.05$) and buprenorphine-exposed infants ($p=.052$). The size of the P1 latencies in response to checks of 69' for buprenorphine-exposed infants did not significantly differ from that of control infants ($p=1.0$). There was more variation in 69' latencies for infants in the MM group than for infants in the other two groups due to two outliers. However, for reasons mentioned above, after sensitivity analyses were conducted it was decided that the latencies for these two infants would be included in analyses. Overall, there was a significant decrease in latencies observed as the size of the stimulus increased [$t(82)=6.05$, $p<.001$].

5.2 Four month VEP latencies adjusting for potential confounding variables

Multiple regression analyses were conducted to examine which variables were the best predictors of P1 latency, and to examine whether prenatal exposure to methadone made a significant contribution to VEP response, whilst adjusting for the effect of potentially confounding variables.

Corrected age was included in the analyses because it correlated significantly with P1 latency (48': $r= .40$, $n=83$, $p<.001$; 69': $r=.44$, $n=85$, $p<.0001$, inverse square transformation). Birth weight, length and HC were not included as covariates because they were all significantly correlated with corrected age. Household income was included as a covariate because it is a strong marker of socioeconomic status. Low socioeconomic status has been associated with poorer developmental outcomes in children (Bor et al., 1997; Petterson & Albers, 2001), while parental social scores have been shown to influence VEP outcome (Makrides, et al., 2000). Fathers' employment status was not included in the multivariable analyses because there was a large amount of missing data for this variable. Neither was accommodation included as a covariate because it was significantly associated with lower family income (Fisher's exact test $p<.01$).

To examine whether prenatal exposure to other substances made a significant contribution to VEP latency, the multivariable analyses were then conducted with the inclusion of the antenatal self-reported substance and drug screen results that differed significantly between groups (Table 5.3). Neither self-reported use of benzodiazepines during pregnancy nor a positive drug screen during pregnancy made any significant contribution to VEP latency to either check size (results not shown). However, self-reported marijuana use during pregnancy made a significant contribution to VEP response to both check sizes and was thus included as a covariate in the final multivariable models.

VEP latency for checks of 48' arc

Variables entered into the model were P1 latency for checks of 48' as the dependent variable, group (with the control group as the reference), corrected age, family income (<$A31, 200 vs >$A31, 200), VEP equipment (1 vs 2), and maternal self-reported marijuana use in pregnancy (yes vs no) as the predictor variables. The model explained 33% of the variance in P1 latency for checks of 48' and was significant at $p<.001$ (Table 5.4). After adjusting for corrected age, family income, VEP equipment and maternal self-reported marijuana use, group status remained a significant predictor of P1 latency for checks of 48' [$F(2,69) = 4.58$, $p=.01$]. After adjusting for covariates, latencies of infants in the MM group remained significantly longer than those of infants in the BM group [$β = -.33$, $t(69)= -2.79$, $p=.01$] and infants in the Control group [$β = -.30$, $t(69)= -2.54$, $p =.01$]. P1 latencies of infants in the BM group did not differ significantly from those of infants in the Control group [$β = .04$, $t(69)= 0.29$, $p=.78$]. After adjusting for the same covariates, corrected age remained significantly associated with P1 latency for checks of 48' and provided the largest unique contribution to the variance in the model. Family income and maternal self-reported use of marijuana in pregnancy also remained significant predictors of P1 latency in response to the 48' arc stimulus. VEP equipment did not provide a significant contribution to the model.

VEP latency for checks of 69' arc

Variables entered into the model were P1 latency for checks of 69' as the dependent variable, group (with the control group as the reference), corrected age, family income (<$A31, 200 vs >$A31, 200), VEP equipment (1 vs 2), and maternal self-reported marijuana use in pregnancy (yes vs no) as the predictor variables. The model explained 34% of the variance in P1 latency for checks of 69' and was significant at $p<.001$ (Table 5.5). After adjusting for group status, family income, VEP equipment and maternal self-reported marijuana use, corrected age remained the significantly associated with P1 latency for checks of 69' arc and provided the largest unique contribution to the variance in the model ($p<.001$). Maternal self-reported use of marijuana in

pregnancy also remained a significant predictor of P1 latency in response to the 69' arc stimulus ($p<.05$). After adjusting for covariates, family income and VEP equipment did not contribute significantly to the model, neither was group status significantly associated with P1 latency for checks of 69' arc [$F(2,70) = 1.45$, $p =.24$].

5.3 Summary of VEP latencies at four months of age

48 minute checks

P1 latency in response to checks of 48' for infants in the MM group were significantly longer than for those of infants in the BM and Control groups, after adjusting for corrected age, family income, VEP equipment and maternal self-reported marijuana use in pregnancy. There was no difference in latencies between infants in the control and BM groups after adjusting for the same covariates. Older corrected age and lower family income were significantly associated with shorter latencies, whilst maternal self-reported use of marijuana in pregnancy remained a significant predictor of longer P1 latencies in response to the 48' arc stimulus.

69 minute checks

P1 latency in response to checks of 69' did not differ significantly between the three groups of infants after adjusting for corrected age, family income, VEP equipment and maternal self-reported marijuana use in pregnancy. Older corrected age was significantly associated with shorter latencies, whilst maternal self-reported use of marijuana in pregnancy remained a significant predictor of longer P1 latencies in response to the 69' arc stimulus.

5.4 Discussion

This is the first study to compare the neurological development, beyond the neonatal period, of infants exposed to methadone or buprenorphine in pregnancy with a control group of non-exposed but matched infants. The key findings were that infants prenatally exposed to

buprenorphine did not differ significantly from non-exposed control infants in terms of their responses to VEP at 4 months of age. In contrast, infants prenatally exposed to methadone had significantly prolonged P1 latencies when compared with both control infants and infants exposed to buprenorphine. These relationships were evident for P1 latencies in response to checks of 48 and 69 minutes of retinal arc. However, after controlling for covariates, the effect of prenatal exposure to methadone was no longer a significant predictor of VEP response to checks of 69'. Latency of the P1 component varies as a function of age and stimulus size. While measurable responses to large checks are present in very young infants, the P1 response to smaller checks is often not evident until a few months of age (Moskowitz & Sokol, 1983). These results suggest that responses to smaller stimuli (which require greater maturation of the visual system) may be more readily influenced by prenatal exposure to methadone.

Older age (corrected for gestation) was associated with significantly shorter P1 latencies for both check sizes, which is consistent with previous evidence that optic neural maturity continues to develop with increasing age (McCulloch, et al., 1999). Also consistent with previous literature (Scher, et al., 1998; Tansley, et al., 1986) was the finding that self-reported maternal use of marijuana during pregnancy was significantly associated with VEP latencies in response to both check sizes. However, P1 latencies were not influenced by maternal self-reported benzodiazepine use or by a positive maternal drug screen in pregnancy. Pharmacological treatment for NAS was not related to VEP outcome in this sample of infants. Infants who lived in a family with an annual income less than $A31,200 had significantly shorter latencies for checks of 48' than infants from higher income families. The direction of this result is counter intuitive and the mechanism underlying this relationship is unclear. The association between family income and shorter P1 latency was not evident for the larger check size.

Whilst corrected age appears to be the strongest predictor of VEP outcome, prenatal exposure to methadone remained a significant predictor of P1 latency in response to checks of 48', and prenatal exposure to marijuana also appears to be a significant predictor of P1 latencies. These finding suggest that infants exposed to methadone in pregnancy may experience delays in visual maturation, as expressed through prolonged VEP P1 latencies, when compared with infants exposed to buprenorphine and non-exposed control infants. Infants prenatally exposed to marijuana in pregnancy may also experience delays in visual development compared to non-marijuana exposed infants.

These findings are consistent with those of previous studies which have found prolonged P1 latencies in infants and young children prenatally exposed to a range of substances (Hansen, et al., 1993; Olegard, et al., 1979; Scher, et al., 1998; Tansley, et al., 1986). Hansen et al. (1993) compared the visual maturity of eight infants exposed to cocaine and amphetamines (*n*=8) to a group of eight non-exposed control infants (mean age 4.5 months). P1 latencies in response to pattern reversal stimuli, subtending 15' arc, were prolonged for the substance-exposed infants, but not significantly different from controls (Hansen, et al., 1993). Scher et al. (1998) assessed the visual maturation of 74 infants prenatally exposed to alcohol, marijuana, tobacco and other unspecified illicit drugs. Prolonged P1 latencies in response to pattern reversal stimuli subtending 50' arc, were evident at four and 18 months of age (Scher, et al., 1998). In a study of 101 children (mean age 48.75 months), Fried and colleagues (1989; 1986) assessed VEPs in response to pattern reversal stimuli subtending 30' arc. The authors reported that prolonged P1 latencies were evident for children exposed to combinations of marijuana, nicotine and alcohol in pregnancy when compared with aged-matched controls (Tansley, et al., 1986).

The results of the present study differ from the animal studies of Pinto et al. (1986) who found no long term effects on the evoked electrical activity of the occipital cortex in rat pups prenatally

exposed to methadone. One explanation for this difference could be that myelination occurs at differing rates in the brains of developing rats and humans. It is recognised that the early postnatal period in the rat is equivalent to the third trimester in human gestation, with the period of brain myelination in rats ending at around postnatal day (PND) 26; it is possible that the age at which the rats in the Pinto et al. study were tested was not equivalent to that of 4-month old human infants (Rice & Barone, 2000; Sanchez, Bigbee, Fobbs, Robinson, & Sato-Bigbee, 2008). It is also possible that the doses of methadone tested in the Pinto et al. study were too low to produce any deleterious effects. Another explanation for this difference is that Pinto et al. used flash stimuli (FVEP) to evoke the potential response whereas the current study used pattern-reversal stimuli (PVEP). PVEP are known to show less inter- and intrapersonal variability in measures of peak latency in normal controls and are also known to be more sensitive than FVEP to lesions of the visual pathways (Aso, et al., 1988; Odom et al., 2004).

The finding in the present study that the P1 latencies of infants exposed to buprenorphine were significantly faster than those of infants exposed to methadone may, in part, be explained by differences in the pharmacology of the two drugs. The PVEP response appears to be generated by neurons in the striate area and, in particular, the generation of the P1 latency is localised in the lateral extrastriate cortex (Algarin, et al., 2003; Aso, et al., 1988; Di Russo, Martínez, Sereno, Pitzalis, & Hillyard, 2002; Ossenblok, Reits, & Spekreijse, 1992). Studies have shown that exposure to opioids during pregnancy can result in a disturbance to the development of selected neurotransmitter systems and, more specifically, that prenatal exposure to methadone decreases Met- and Leu-enkephalin levels in the striatum (Tiong & Olley, 1988).

Another explanation for the differences in the VEP outcome observed between the two groups of drug-exposed infants in the present study may be related to placental transfer of the individual drugs. The higher incidence of NAS that has been observed in methadone-exposed infants may be

due to increased placental transfer as pregnancy progresses (Kandall, Doberczak, Jantunen, & Stein, 1999); whereas the low placental transfer of buprenorphine and the comparatively low concentration of buprenorphine in the foetal circulation may account for a reduced incidence of NAS (Nanovskaya, et al., 2002). A decrease in neuronal firing rates has been demonstrated with exposure to opioids *in vitro* (Pepper & Henderson, 1980), and it is possible that the greater placental transfer of methadone may have the effect of inhibiting neuronal firing in the striate cortex where the VEP response is generated. As mentioned, prenatal exposure to methadone, but not to buprenorphine, decreases levels of the opioid peptide enkephalin in the striatum (Tiong & Olley, 1988), where the generation of the P1 latency is localised (Algarin, et al., 2003; Aso, et al., 1988). It has also been demonstrated that perinatal exposure to buprenorphine affects myelination and axonal growth in the developing rat brain (Sanchez, et al., 2008).

The predictive value of the delayed P1 response observed in the methadone (and marijuana) exposed infants in this sample is unclear in terms of its clinical relevance. Kato and Watanabe (2006) conducted a review of studies on the predictive value of FVEPs in newborn infants. They concluded that FVEPs were a good predictor of neurological development at 18-24 months in full-term infants with birth asphyxia, but that their predictive value in preterm infants was unclear (Kato & Watanabe, 2006). Iinuma, Lombroso and Matsumiya (1997) found that FVEP waveforms were predictive of later visual development in 56 infants with early visual inattentiveness (Iinuma, et al., 1997). To my knowledge there has been no previous literature evaluating the prognostic value of VEP in drug-exposed children. Changes in visual maturation appear to continue to develop well into childhood (Hansen, et al., 1993; Moskowitz & Sokol, 1983) and myelination of the optic nerve may continue until at least 5 years of age (Moskowitz & Sokol, 1983; Taylor & McCulloch, 1992). Previous research has found that early differences in FVEP P1 latencies of preterm and term infants were no longer observable at six months post-birth (Uysal, Renda,

Topcu, Erdem, & Karacan, 1993); while Scher et al. (1998) found transient delays in visual maturation in infants with prenatal substance exposure.

This suggests that the apparent delays observed in the present study for infants prenatally exposed to methadone and/or marijuana may be only temporary. Infants' responses to VEP will be re-assessed at 36 months of age as part of the longitudinal study protocol. Results from this assessment may assist in determining whether the difference in visual maturation, observed between the drug-exposed groups at four months of age, remains in later childhood.

Although research to date supports the short-term safety and efficacy of buprenorphine during pregnancy and the early neonatal period (Fischer, et al., 2006; Jones, et al., 2005; Kakko, et al., 2008), studies where the longer term outcome of children exposed to buprenorphine has been systematically documented have yet to be published. Overall, this research provides new information regarding the neurological outcome of four month old infants prenatally exposed to buprenorphine or methadone. Results suggest that maternal maintenance with buprenorphine appears to offer an advantage over methadone in terms of infant neural development at four months of age. Further research, incorporating larger sample sizes and more rigorous study designs, should be undertaken to compare the neurological development of infants exposed to buprenorphine or methadone during pregnancy.

CHAPTER 6

Bayley Scales of Infant Development

This chapter describes the cognitive, psychomotor and behavioural development of infants, assessed at 12 months, and 24 months of age, as measured on the Bayley Scales of Infant Development – Second Edition (BSID-II). First, development of each of the three groups of infants, in terms of their scores on the Mental Developmental Index (MDI), Psychomotor Developmental Index (PDI) and Behavior Rating Scale (BRS), were compared. Next, relationships between potential confounding variables and the three BSID-II scores were examined, and differences in scores between groups were then analysed adjusting for significant confounding variables. Finally, change in BSID-II over time was examined across the three groups of infants.

The present chapter addresses the following hypotheses:

Hypothesis 6:

The mean cognitive, psychomotor and behavioural development scores of infants prenatally exposed to buprenorphine will not differ significantly from those of a non-exposed control group, when assessed at 12 and 24 months of age.

Hypothesis 7:

The cognitive, psychomotor and behavioural development scores of infants prenatally exposed to methadone will be significantly lower than those of infants prenatally exposed to buprenorphine and a non-exposed control group of infants, when assessed at 12 and 24 months of age.

Hypothesis 8:

Change in cognitive, psychomotor and behavioural development scores over time will not vary significantly between children prenatally exposed to buprenorphine, methadone, or in a non-exposed control group.

Statistical analyses

Analyses were conducted according to the methods described in Chapter 2, section 2.7, and previously outlined in the statistical analyses section of Chapter 4.

A series of simple linear regression analyses and ANOVAs were conducted to examine the contribution of independent variables to MDI, PDI and BRS scores at 12 and 24 months of age. Standard multiple regression analyses were then conducted to examine the contribution of each independent variable to the individual BSID outcomes, whilst adjusting for the effect of the other variables in the model. A series of split-plot ANOVAs were undertaken to examine whether mean BSID scores changed over time and whether change in mean scores varied between infants in each of the three groups. The between-subjects factor was group (control, BM and MM) and the within-subjects factor was assessment time (12 and 24 months). Total HOME score was entered as a covariate.

6.1 Bayley Scales of Infant Development at 12 months of age

Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores of the Bayley Scales of Infant Development – Second Edition (BSID-II) were available for all participating infants except two (both male) at the 12-month follow-up assessment. One infant in the BM group was too tired to participate in the assessment at the scheduled time and the family could not be contacted to make another appointment, and one in the MM group did not undergo assessment on the BSID-II as the family had moved away from the study area. Thus data for mental and motor development at 12 months of age were available for 81/83 children (98%). Behavior Rating Scale (BRS) scores were available for ninety percent (75/83) of participating infants at the twelve month follow-up assessment. BRS data were not collected for eight infants (three in each of the control and BM groups, and two in the MM group) at the 12-month assessment, as it was inadvertently omitted. This omission was not systematic and it was not

possible to go back and re-assess the infants' behaviour. The 12-month MDI variable was negatively skewed when compared across the three groups of infants and was squared for use in parametric analyses.

Mental Developmental Index (MDI)

The MM group had the highest mean MDI score at 12 months of age and the BM group had the lowest mean score (Table 6.1). However, with a small effect size of η^2= .04, the actual difference in mean scores was quite small, and the difference was not statistically significant [F(2,78)=1.43, p=.25, square transformation]. Overall, the majority of infants (88%) obtained a score 'Within Normal Limits' (Index score of 85-114). Five infants (three controls and one in each of the BM and MM groups) obtained MDI scores in the 'Accelerated Performance' range (Index score ≥115, ≥1 *SD* above the standardised mean of 100), while five (two control and three BM) obtained scores in the 'Mildly Delayed' range, < 1 *SD* below the standardised mean (Index score ≤85). These infants presented with high activity levels, poor concentration, or were difficult to engage, and parental reports of their behaviour on the day of testing were noted to be 'typical' or 'very typical' of their usual behaviour. Four of the infants scored 'Within Normal Limits' on the MDI at 24-months of age, whilst one male infant in the BM group continued to score in the Mildly Delayed range.

Psychomotor Developmental Index (PDI)

Table 6.1 shows that 12-month PDI scores for infants in the MM group were approximately four points lower than infants in either of the other two groups. The effect size was small to medium (η^2= .03) and the difference in scores was not statistically significant [F(2,78)=1.31, p=.28]. The majority of infants in the study (80%) obtained a PDI score 'Within Normal Limits', however 15% (six controls, two BM and four MM) obtained a score in the 'Mildly Delayed Performance' range. The overall mean score of 91.64 (*SD*=10.03), while still well within normal limits, is almost two thirds of a *SD* below the standardised mean of 100. The 95% confidence interval (CI) indicates that

there is a 95% chance that the true mean PDI score for this sample of infants would fall within the range 89.4-93.9. The BSID-II manual suggests that individual scales of the BSID-II are not necessarily predictive of later cognitive functioning, particularly when assessed prior to the age of two years (Bayley, 1993).

Behavior Rating Scale (BRS)

Infants in the BM group scored slightly higher on the BRS at 12 months of age than infants in the other two groups (Table 6.1). Again, the effect size was small to medium (η^2= .04) and the difference in scores was not statistically significant [$F(2,72)=1.55$, $p=.22$]. Overall 83% of infants scored 'Within Normal Limits' (≥26th percentile) for their age group. However 15% of the sample (five controls, three BM, three MM) scored within the 'Questionable' range and two infants in the MM group scored in the 'Non-Optimal' range (≤10th percentile) for their age. Males were more likely to obtain a behaviour score below the 25th percentile for their age group, compared with females (26% vs. 8%, Fisher's exact test p =.07).

6.1.1 Relationship between 12-month Bayley Scale scores and potential confounding variables

Cognitive development at 12 months of age was significantly associated with maternal social support at four months of age, [β = .26, $t(79)$ = 2.38, p <.05, cubic transformation], with higher MDI scores associated with higher levels of perceived support (ISSI-SF Total scores). Higher infant MDI scores at 12 months of age were also significantly associated with a more optimal home environment (higher Total HOME score) at 12 months of age [β = .30, $t(78)$ = 2.74, p <.01, cubic transformation]. While higher MDI scores were associated with lower levels of parenting stress (lower Parenting Stress Index scores) at 12 months of age, this relationship did not reach conventional levels of statistical significance [Spearman's rho= -.21, n=75, p=.07].

Psychomotor development at 12 months of age was significantly associated with birth HC [β = .27, t(79) = 2.36, p <.05, power 0.9 transformation], with higher PDI scores associated with larger HC at birth. The relationship between 12-month PDI scores and the following independent variables did not reach traditional levels of statistical significance: maternal self-reported use of alcohol in pregnancy [Kruskal-Wallis: χ^2 (1) = 3.21, n= 78, p=.07], and birth weight [β = .21, t(78) = 1.90, p =.06, power 0.4 transformation].

Behaviour scores at 12 months of age were significantly associated with infant gender, with girls scoring significantly more highly than boys on the BRS at 12 months of age [Kruskal-Wallis: χ^2 (1) = 8.03, n= 75, p<.01]. Higher home environment scores at 12 months of age [β = .31, t(72) = 2.78, p <.01, log transformation] and better perceived maternal social support at four months of age [Spearman's rho=.26, n=66, p<.05] were also significantly associated with higher BRS scores at 12 months of age. The median BRS12 score of infants whose mothers had completed high school was higher than that of infants whose mothers had not completed high school, although this difference did not reach a traditional level of statistical significance [Kruskal-Wallis: χ^2 (1) = 3.46, n= 75, p=.06].

6.1.2 Twelve month Bayley Scale scores adjusting for potential confounding variables
Twelve month Mental Developmental Index Scores
Variables entered into the model were 12-month MDI as the dependent variable (power 2.5 transformation), with maternal social support (ISSI-SF Total score) at four months of age, Total HOME score at 12 months of age, and group (with the control group as the reference) as the predictor variables. The model explained 18% of the variance in MDI scores at 12 months of age and was significant at p<.01 (Table 6.2). Total HOME Score at 12 months of age remained significantly associated with 12-month MDI scores and provided the largest unique contribution to the variance in the model. After adjusting for covariates, the association between maternal

social support at four months of age and MDI at 12 months of age did not quite reach traditional statistical significance (p=.06). Group status was weakly associated with 12-month MDI [$F_{(2,75)}$ = 2.42, p =.10, η^2 = .05], and this was largely due to the difference between the MM group and the BM group [β = .26, $t(75)$ =2.20, p =.03]. Scores of infants in the control group did not differ significantly from those of infants in the BM group [β =-.12, $t(75)$ = -0.99, p = .33], or the MM group [β =.16, $t(75)$ = 1.34, p = .18].

Twelve month Psychomotor Developmental Index Scores

Variables entered into the model were 12-month PDI as the dependent variable (square transformation), with birth HC and group (with the control group as the reference) as the predictor variables. The model explained nine percent of the variance in PDI scores at 12 months of age (Table 6.3), but did not reach traditional levels of statistical significance (p=.06). Infants' HC at birth remained significantly associated with 12-month PDI score and provided the largest unique contribution to the variance in the model. After adjusting for birth HC, group status was not significantly associated with 12-month PDI [$F_{(2,77)}$ = 0.67, p =.52].

Twelve month Behavior Rating Scale Scores

Variables entered into the model were 12-month BRS as the dependent variable (square root transformation), with gender (with girls as the reference), ISSI-SF Total score at four months of age, Total HOME score at 12 months of age, and group (with the control group as the reference) as the predictor variables. The model explained 22% of the variance in BRS scores at 12 months of age and was significant at p<.01 (Table 6.4). After adjusting for covariates, gender remained a significant predictor of BRS at 12 months of age (p<.01) and provided the largest unique contribution to the variance in the model. Total HOME score at 12 months of age provided the next largest unique contribution to the variance in the model and remained significantly associated with BRS at 12 months of age (p<.05). After adjusting for covariates, neither maternal

social support at four months of age, nor group status [$F_{(2,68)}$= 1.26, p =.29] was significantly associated with BRS at 12 months of age.

6.1.3 Summary of Bayley Scale scores at 12 months of age

Mental Developmental Index

MDI scores at 12 months of age were significantly higher in the MM group compared with the BM group, after adjusting for perceived maternal social support at four months of age and home environment at 12 months of age. There was no difference in 12-month MDI scores between the control group and infants in either of the other two groups after adjusting for the same covariates. Higher HOME scores (indicating a more optimal home environment) remained significantly associated with higher MDI scores at 12 months of age.

Psychomotor Developmental Index

PDI scores at 12 months of age did not differ significantly between the three groups of infants, after adjusting for HC at birth. Larger birth HC remained significantly associated with higher PDI scores at 12 months of age.

Behavior Rating Scale

BRS scores at 12 months of age did not differ significantly between the three groups of infants, after adjusting for gender, perceived maternal social support at four months of age and home environment at 12 months of age. Gender remained a significant predictor of BRS scores at 12 months of age (p<.01), with girls achieving significantly higher BRS scores than boys. Higher HOME scores (indicating a more optimal home environment) remained significantly associated with higher BRS scores at 12 months of age.

6.2 Bayley Scales of Infant Development at 24 months of age

Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores of the

Bayley Scales of Infant Development – Second Edition (BSID-II) were available from all 73

participating infants at the 24-month follow-up assessment. Behavior Rating Scale (BRS) scores

were available for ninety percent (66/73) of infants at this assessment. BRS data for seven infants

(one in the control group, four in the BM group, and two in the MM group) were not collected at

the 24-month assessment, as it was inadvertently omitted. The 24-month MDI variable was

skewed and a suitable transformation could not be found, thus Kruskal-Wallis tests were used to

examine differences between group medians.

Mental Developmental Index (MDI)

MDI scores at 24 months of age ranged from 61 to 118. A Kruskal-Wallis test, corrected for tied

ranks, showed that at 24 months of age the rankings of MDI scores across the three groups were

not significantly different [χ^2 (2) = 2.75, *n*= 73, *p*=.25]. The proportion of variability in the ranked

dependent variable accounted for by group was η^2=.04, indicating a small effect of group

membership on MDI at 24 months of age. Mann-Whitney U tests were conducted to evaluate

pair-wise differences between the three groups. Table 6.1 shows that, at 24 months of age, there

was no significant difference in median MDI scores between infants in the MM group and the

control group (*z* = 0.21, *p* =.84). Neither was there a significant difference in median MDI at 24

months of age between infants in the BM and MM groups (*z* = -1.22, *p* =.22). The median MDI of

infants in the BM group was lower than infants in the control group although this difference did

not reach statistical significance (*z* = 1.57, *p* =.12). Nearly two thirds of infants in the study (65%)

obtained a score 'Within Normal Limits' (Index score of 85-114) on the MDI at 24 months of age.

Four infants (two males and two females, all in the control group) obtained scores in the

'Accelerated Performance' range on the MDI at 24 months of age. Nineteen infants (eight

controls, eight BM and three MM) obtained scores in the 'Mildly Delayed' range, while three

female infants (two BM and one MM) scored <2 *SD* below the standardised mean, in the 'Significantly Delayed' range. Both children in the BM group with scores within the 'Significantly Delayed' range presented with high activity levels, poor concentration, and were difficult to engage on the day of assessment. Parental reports of these infants' behaviour on the day of testing were noted to be 'typical' or 'very typical' of their usual behaviour. One child obtained scores 'Within Normal Limits' when retested at 36 months of age, but later test scores were not available for the second child. The child in the MM groups was also very difficult to engage when tested at 24 months of age. She showed little interest in the test items and appeared to have difficulty understanding verbal instructions. Her mother reported that this behaviour was 'very typical' of the child in question, and that results from a speech and language assessment, unrelated to the present study, were pending.

Psychomotor Developmental Index (PDI)

Infants in the control group achieved slightly higher scores than infants in either of the other two groups on the PDI at 24 months of age (Table 6.1). The effect size was small (η^2= .02) and the difference in mean scores was not statistically significant [F(2,70)=0.54, p=.59]. Forty eight infants (66%) obtained a PDI score 'Within Normal Limits' and six percent (two controls and one each in the BM and MM groups) scored within the 'Accelerated Performance' range. Thirty percent of infants scored below average for their age range, with 23 percent (seven controls, seven BM and three MM) scoring in the 'Mildly Delayed Performance' range and six percent (one control, one BM and two MM) scoring in the 'Significantly Delayed' range.

Behaviour Rating Scale (BRS)

There was no significant difference in BRS scores between the three groups of infants at 24 months of age (Table 6.1). The effect size was very small (η^2= .005) and the difference in scores was not statistically significant [F(2,63)=0.17, p=.84]. Overall 73 percent of infants scored 'Within

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Normal Limits' (≥26th percentile) for their age group, 17 percent of the sample (eight controls, one BM, two MM) scored within the 'Questionable' range, and 11 percent (4 BM and 3 MM) scored in the 'Non-Optimal' range (≤10th percentile) for their age. Female infants were slightly more likely to obtain a score below the 25th percentile for their age group than males (32% compared with 23%), although this difference was not significant [χ^2 (1) =0.73, *n*= 66, *p*=.39].

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

Cognitive development at 24 months of age was significantly associated with maternal self-reported use of benzodiazepines in pregnancy [Kruskal-Wallis: χ^2 (1) = 7.54, *n*= 73, *p*<.01], with infants whose mothers reported use of benzodiazepines achieving significantly lower MDI scores than infants whose mothers reported no use of benzodiazepines. Higher MDI scores at 24 months of age were significantly associated with (1) higher perceived levels of maternal social support at four months of age (higher ISSI-SF Total scores) [Spearman's rho = 0.33, n= 73, *p*<.01], (2) higher HOME scores (indicating more optimal home environment) at 24 months of age [Spearman's rho = 0.44, n= 67, *p*<.001], and (3) lower scores on the PSI Parent Domain (indicating lower levels of parenting stress) at 24 months of age [Spearman's rho = -0.36, n= 61, *p*<.01].

Psychomotor development at 24 months of age was significantly associated with maternal self reported use of marijuana in pregnancy [Kruskal-Wallis: χ^2 (1) = 4.39, *n*= 72, *p*<.05] and maternal self-reported use of benzodiazepines in pregnancy [F(1,71)=11.57, *p*<.01, log transformation], with infants whose mothers reported use of marijuana or benzodiazepines achieving significantly lower PDI scores than infants whose mothers reported no use of marijuana or benzodiazepines. Higher 24-month PDI scores were significantly associated with (1) higher ISSI-SF Total scores at four months of age [β = .36, *t*(71) = 3.22, *p* <.01, power 0.7 transformation], (2) higher HOME scores at 24 months of age [β = .14, *t*(65) = 3.37, *p* <.01, power 0.6 transformation], and (3) lower

scores on the PSI Parent Domain at 24 months of age [β = .33, $t(59)$ = 2.67, p <.01, power -0.3 transformation] .

Higher BRS scores at 24 months of age were significantly associated with (1) higher ISSI-SF Total scores at four months of age [Spearman's rho = 0.26, n= 66, p <.05], (2) higher HOME scores at 24 months of age [β = .31, $t(59)$ = 2.49, p <.05, power 0.9 transformation], and (3) lower scores on the PSI Parent Domain at 24 months of age [β = -.34, $t(53)$ = -2.66, p <.05, power 0.9 transformation] .

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

Twenty four month Mental Developmental Index Scores

Variables entered into the model were 24-month MDI as the dependent variable (square transformation), with maternal self-reported use of benzodiazepines in pregnancy, ISSI-SF Total score at four months of age, Total HOME score at 24 months of age, and group (with the control group as the reference) as the predictor variables. The model explained 30% of the variance in Mental Developmental Index Scores at 24 months of age and was significant at p <.001 (Table 6.5). After adjusting for covariates, Total HOME score at 24 months remained significantly associated with cognitive development at 24 months of age (p <.01) and provided the largest unique contribution to the variance in the model. Maternal use of benzodiazepines in pregnancy provided the next largest unique contribution to the variance in the model and remained significantly associated with MDI score at 24 months of age (p <.05). After adjusting for covariates, maternal social support at four months of age was no longer significantly associated with cognitive development at 24 months of age, neither was group status significantly associated with 24-month MDI [$F(2,61)$ = 0.24, p =.79].

PSI Parent Domain Total score at 24 months of age was not included in the multivariable analysis because it was significantly correlated with ISSI-SF Total score at four months of age [r = -.67, n= 61, p <.0001]. There was also a large amount of missing data for this variable and its inclusion in the multiple regression analysis considerably reduced the available sample size. When PSI Parent Domain Total score at 24 months of age replaced ISSI-SF Total score in the model, the overall results remained similar and it did not make a significant contribution to the model (results not shown), and therefore was not included in the final analyses.

Twenty four month Psychomotor Developmental Index Scores

Predictors included in the model were maternal self-reported use of benzodiazepines in pregnancy, ISSI-SF Total score at four months of age, Total HOME score at 24 months of age, and group (with the control group as the reference). As with the previous regression, the PSI Parent Domain Total score at 24 months of age was not included in the 24-month PDI multivariable analyses. The model explained 31% of the variance in Psychomotor Developmental Index Scores at 24 months of age and was significant at p <.001 (Table 6.6). After adjusting for covariates, HOME score at 24 months of age remained significantly associated with psychomotor development at 24 months of age (p <.01) and provided the largest unique contribution to the variance in the model. Maternal self-reported use of benzodiazepines in pregnancy provided the next largest unique contribution to the variance in the model and remained significantly associated with psychomotor development at 24 months of age (p <.01). After adjusting for covariates, maternal social support at four months of age did not retain a significant association with PDI score at 24 months of age. Neither did group status provide a significant contribution to the model [$F(2,61)$ = 0.28, p =.76].

Maternal self-reported use of marijuana in pregnancy was not included in the same multivariable analysis as maternal self-reported use of benzodiazepines because the two variables were

significantly associated with one another [χ^2(1)=4.10, p=.04]. When maternal self-reported use of marijuana during pregnancy replaced maternal self-reported use of benzodiazepines in the model, the overall results remained similar and it did not make a significant contribution to the model (results not shown). Additionally, when PSI Parent Domain Total score at 24 months of age replaced ISSI-SF Total score in the model, the overall results remained similar and it did not make a significant contribution to the model (results not shown).These variables were therefore not included in the final analyses.

Twenty four month Behavior Rating Scale Scores

Twenty four month BRS was normalised using a power 2.5 transformation. ISSI-SF Total score at four months of age, Total HOME score at 24 months of age, and group (with the control group as the reference) were examined as independent predictor variables. As previously, PSI Parent Domain Total score at 24 months of age was not included in the multivariable analyses. The model explained 15% of the variance in BRS scores at 24 months of age and was significant at p<.05 (Table 6.7). After adjusting for covariates, Total HOME score at 24 months remained significantly associated with behaviour at 24 months of age (p<.05) and provided the largest unique contribution to the variance in the model. After adjusting for covariates, maternal social support at four months of age did not provide a significant contribution to BRS scores at 24 months of age. Neither was group status significantly associated with 24-month behaviour F(2,56) = 0.99, p =.38]. When PSI Parent Domain Total score at 24 months of age replaced ISSI-SF Total score in the model, the overall results remained similar and it did not make a significant contribution to the model (results not shown) and therefore was not included in the final analyses.

6.2.3 Summary of Bayley Scale scores at 24 months of age

Mental Developmental Index

MDI scores did not differ significantly between the three groups of infants at 24 months of age, after adjusting for maternal self-reported use of benzodiazepines in pregnancy, perceived maternal social support (ISSI-SF Total Scores) at four months of age, and home environment scores at 24 months of age. Maternal self-reported use of benzodiazepines in pregnancy was significantly associated with lower infant MDI scores at 24 months of age, while higher HOME scores (indicating a more optimal home environment) at 24 months of age remained significantly associated with higher MDI scores at 24 months of age.

Psychomotor Developmental Index

PDI scores did not differ significantly between the three groups of infants at 24 months of age, after adjusting for maternal self-reported use of benzodiazepines in pregnancy, perceived maternal social support at four months of age, and HOME scores at 24 months of age. Maternal self-reported use of benzodiazepines was significantly associated with lower PDI scores at 24 months of age, as were higher HOME scores at 24 months of age.

Behavior Rating Scale

BRS scores did not differ significantly between the three groups of infants at 24 months of age, after adjusting for perceived maternal social support at four months of age, and HOME scores at 24 months of age. Higher HOME scores at 24 months of age remained significantly associated with higher BRS scores at 24 months of age, although maternal social support at four months of age was no longer significantly associated with BRS at 24 months of age.

6.3 Longitudinal analyses of Bayley Scale Index Scores

Figures 6.1-6.3 show the mean BSID-II scores of each group over the two follow-up assessments. A series of split-plot analyses of variance (ANOVA) were undertaken to examine whether change in mean BSID-II scores (MDI, PDI and BRS) over time varied between the three groups of infants. For each split-plot ANOVA, the between-subjects factor was group (control, BM and MM) and the within-subjects factor was time (12 and 24 month follow-up assessments). Total HOME score was entered as a covariate in each model. Preliminary checks were conducted to ensure that there was no violation of the assumptions of normality, linearity, homogeneity of variances, and homogeneity of regression slopes.

Mental Developmental Index Scores

After adjusting for total HOME score, the ANOVA showed that there was a statistically significant main effect for time [$F(1,62)=16.68$, $p<.0001$], with a moderate effect size ($\eta^2=.09$). MDI scores of infants in the study significantly decreased over the 12 and 24 month follow-up assessments and the ANOVA indicated that time accounted for nine percent of the variance in MDI scores. The ANOVA showed no significant main effect for group [$F(2,78)=0.14$, $p=.87$, $\eta^2=.002$], and total HOME score was of marginal statistical significance [$F(1,78)=3.74$, $p=.06$, $\eta^2=.02$]. Additionally, the time × group interaction did not reach statistical significance [$F(2,62)=1.24$, $p=.30$, $\eta^2=.01$], suggesting that changes in mean MDI score over the 12 and 24 month follow-up assessments did not vary significantly between the three groups of infants. The model was repeated with the inclusion of maternal self-reported use of benzodiazepines in pregnancy as a covariate. However this did not change the overall outcome and the main effect of maternal self-reported benzodiazepine use was not statistically significant [$F(1,77)=0.94$, $p=.34$, $\eta^2=.01$].

Psychomotor Developmental Index Scores

After adjusting for total HOME score, there was no significant main effect for time [$F(1,62)=0.01$, $p<.91$, $\eta^2<.0001$] or group [$F(2,78)=0.94$, $p=.39$, $\eta^2=.01$]. The ANOVA showed that there was a statistically significant main effect for total HOME score [$F(1,78)=5.26$, $p<.05$], although the effect size was small ($\eta^2=.04$,) indicating that total HOME score accounted for only four percent of the variance in PDI scores. In addition, the time × group interaction did not reach statistical significance: $F(2,62)=0.19$, $p=.82$, $\eta^2<.01$], indicating that changes in mean PDI scores over the 12 and 24 month follow-up assessments did not vary significantly between the three groups of infants.

Behavior Rating Scale Scores

After adjusting for total HOME score, there was a significant main effect for time [$F(1,51)=105.58$, $p<.0001$] , with a large effect size ($\eta^2=.33$). Overall, mean BRS scores decreased significantly over the 12 and 24 month follow-up assessments, and time accounted for 33% of the variance in BRS scores. There was no significant main effect for group [$F(2,77)=0.99$, $p=.38$, $\eta^2=.01$], and the main effect for total HOME score was of marginal significance [$F(1,77)=3.24$, $p=.08$, $\eta^2=.02$]. The time × group interaction did not reach statistical significance [$F(2,51)=0.45$, $p=.64$, $\eta^2=.003$], suggesting that change in BRS over time did not vary significantly between the three groups of infants. The model was repeated with the inclusion of infant gender as a covariate, however this did not change the overall outcome and the main effect of gender was not statistically significant [$F(1,76)=0.11$, $p=.74$, $\eta^2<.001$].

6.3.1 Summary of Bayley Scale longitudinal analyses

Results of the three split-plot ANOVAs supported the hypothesis that change in each of the Bayley Scale scores over time would not vary significantly between infants prenatally exposed to buprenorphine, methadone or the non-exposed control group of infants. There was a significant main effect of time for the Mental Developmental Index and Behavior Rating Scale scores, illustrating that mean scores on both of these measures decreased significantly between the 12 and 24 month assessments. There was a statistically significant main effect of total HOME score for the Psychomotor Developmental Index, demonstrating that higher total HOME scores (indicating a better quality of Home Environment) were associated with better psychomotor development. However, none of the interactions between group status and time were significant, indicating that change in Bayley Scale scores over the three follow-up assessments did not differ significantly between the three groups of infants.

6.4 Discussion

This chapter compared the cognitive, psychomotor and behavioural development of infants prenatally exposed to methadone or buprenorphine, with that of a group of non-exposed infants. Overall, scores on the Mental Developmental Index (MDI), Psychomotor Developmental Index (PDI) and the Behaviour Rating Scales (BRS) of the Bayley Scales of Infant Development did not differ significantly between infants prenatally exposed to buprenorphine, methadone, or a non-exposed control group. A small difference found between the MM and BM groups on the 12-month MDI in multivariable analysis will be discussed below. As hypothesised, change in Bayley Scale scores over time did not vary significantly between the three groups of infants. This was expected, as while previous research has reported significant changes in BSID-II scores during infancy and toddlerhood, substance exposure was not found to be significantly associated with change in scores over time (Messinger, et al., 2004).

As described in Chapter 4, the opioid system is involved in growth and development, and animal studies have shown that exposure to opioids during pregnancy can result in a disturbance to the development of selected neurotransmitters in the CNS. In terms of how this may affect the cognitive and motor development of infants, research examining the role of neurotransmitters in brain development has shown that dopamine regulates the growth and branching of neuronal axons and dendrites. Dopamine is therefore important in terms of executive functioning, such as planning and problem solving, along with motor performance (Herlenius & Lagercrantz, 2004). Perinatal exposure to methadone can result in disruption to the dopaminergic system in the frontal cortex, and reduced dopamine concentrations in both the forebrain and the striatum (Konijnenberg & Melinder, 2011; Robinson, Maher, Wallace, & Kunko, 1997). Prenatal exposure to methadone has also been shown to increase levels of serotonin in the parietal cortex, and reduce norepinephrine levels in the hippocampus. Serotonin is involved in the coordination of sensory and motor responses, whilst norepinephrine is responsible for regulating neuronal growth and may be involved in attention and memory functions (Herlenius & Lagercrantz, 2004; Konijnenberg & Melinder, 2011; Robinson, et al., 1997). Additionally, previous research has suggested that opioids may act indirectly upon the cholinergic system, which in the CNS is responsible for regulation of spatial working memory, visual discrimination learning, and visual attention (Everitt & Robbins, 1997; Robinson, 2000, 2002; Wu, et al., 2001). Thus, prenatal exposure to opioids may affect a number of systems in the developing brain with subsequent deleterious effects on cognitive and psychomotor development and behaviour.

Mental Developmental Index

In the current study, infants prenatally exposed to methadone achieved the highest mean score on the MDI at 12 months of age, approximately two points higher than the non-exposed control group, and five points higher than the mean score of infants prenatally exposed to buprenorphine. After adjusting for perceived maternal social support at four months of age and

12-month home environment, MDI at 12 months of age was significantly higher in the MM group compared with the BM group. However, this difference was not evident in univariable analyses, neither was it found at 24-months of age. Given the small effect size and lack of consistency with other results, this may have well reached statistical significance through multicollinearity and may be of little clinical significance. As described in detail below, all other studies have found either no significant differences in MDI scores, between methadone-exposed and non-exposed infants, or have reported significantly lower MDI scores for infants prenatally exposed to methadone. In the current study, MDI did not differ significantly between the control group and the two substance-exposed groups after adjusting for covariates. Higher MDI at 12 months of age remained significantly associated with a more enriched home environment.

Infants in the MM group had higher median scores on the 24-month MDI than infants in the BM group, although this difference was not statistically significant. Median MDI scores of infants in the MM group were similar to those for infants in the control group. Although the median 24-month MDI score of infants in the BM group was almost 10 points below that of infants in the MM and control groups, the range of scores for each of the three groups was similar. When prenatal exposure to benzodiazepines, perceived maternal social support at four months of age and current home environment were included in the analyses, prenatal exposure to benzodiazepines remained significantly associated with lower MDI scores, and a more enriched home environment remained significantly associated with higher MDI scores at 24 months of age.

The finding that infants prenatally exposed to methadone achieved the highest scores on the MDI was unexpected. Whilst there are no previous studies comparing cognitive outcomes on the MDI between buprenorphine- and methadone-exposed infants, five research groups have reported no statistically significant differences in MDI scores between infants prenatally exposed to methadone and non-exposed comparison groups, although scores of infants prenatally exposed

to methadone have generally been lower than their non-exposed peers (see Chapter 1) (Bernstein & Hans, 1994; Chasnoff, et al., 1984; Hans, 1989; Messinger, et al., 2004; Wilson, 1989; Wilson, et al., 1981). Chasnoff et al. found no differences in mean BSID scores between 39 infants prenatally exposed to methadone, 19 poly-drug exposed infants and 27 non-exposed infants at 3, 6, 12 and 24 months of age (Chasnoff, et al., 1984). Similarly, Wilson and colleagues reported no significant differences in MDI performance at nine, 18 or 24 months of age, between 39 methadone-exposed infants and 57 non-exposed comparison infants (Wilson, 1989; Wilson, et al., 1981). Bernstein and Hans reported that 24-month MDI scores for 30 methadone-exposed infants and 44 non-drug exposed infants did not differ significantly (Bernstein & Hans, 1994; Hans, 1989), whilst van Baar and colleagues (van Baar, 1990; van Baar, Fleury, & Ultee, 1989; van Baar, et al., 1994) also found no significant differences between MDI scores, at 6, 12 and 18 months of age, for 35 infants prenatally exposed to methadone and 37 non-exposed infants (van Baar, 1990; van Baar, Fleury, & Ultee, 1989; van Baar, et al., 1994). Messinger et al. (2004) found that, in univariable analyses, the mean 12-month MDI of infants prenatally exposed to opioids (n =79) was significantly lower than non-opioid exposed infants (n=960); however mean MDI scores at two and three years of age did not differ significantly between the two groups. After adjusting for covariates, no significant effect of opioid exposure remained on overall MDI performance (Messinger, et al., 2004).

On the other hand, five research groups have reported significantly lower scores on the MDI for infants exposed to methadone, compared with non-exposed infants at varying ages (Chasnoff, 1985; Chasnoff, et al., 1986; Hunt, et al., 2008; H. L. Johnson, et al., 1987, 1990; H. L. Johnson & Rosen, 1982; Lodge, et al., 1975; Rosen & Johnson, 1982; van Baar, 1990; van Baar, Fleury, & Ultee, 1989). Some of the reasons for this contrast in results may be inadequate control for confounding factors, conception whilst on heroin, or exposure to poly-substance abuse. It is useful to consider these studies in more detail to appreciate the methodological differences.

Chasnoff and colleagues (1985; 1986) found that MDI scores of 26 opioid-exposed infants were significantly lower than those of 29 non-exposed controls at six and 12 months of age. The authors noted that the majority of the opioid-exposed infants were conceived whilst their mothers were using heroin, but were also exposed to maternal methadone maintenance during pregnancy. A smaller number of opioid-exposed infants were prenatally exposed to a combination of pentazocine (a synthetic mixed agonist/antagonist narcotic) and tripelennamine (an antihistamine) which, when taken together, are known as "T's and blues". The lower scores of these infants may have been due to exposure to high doses of opioids, or the combination of substances may have contributed to the infants' poorer performance on the MDI assessment.

Lodge et al. (1975) found that infants prenatally exposed to heroin and/or methadone (n=29) achieved lower MDI scores than non-exposed infants (n=10) when tested at approximately one-month of age. They suggested that this was due to poorer orientation and lower visual attentiveness in the opioid-exposed group. The lower scores of the opioid-exposed infants were possibly due to the very low MDI scores of the infants prenatally exposed to a combination of methadone and heroin (n=6, $M\pm SD$=83.33±9.21). The authors suggested that these infants may have been exposed to a higher overall dose of narcotics, however, due to the small study numbers it was suggested that the results be interpreted with caution (Lodge, et al., 1975). Another possibility for the lower MDI scores for the opioid-exposed infants may have been due to the timing of assessment. When tested, the opioid-exposed infants in Lodge et al.'s study may still have been recovering from NAS symptoms which could have affected the infants' performance on developmental assessments. Additionally, over half of the opioid-exposed sample was treated for NAS with combinations of benzodiazepines and phenobarbital, both of which are known to adversely affect brain development and cognitive performance (Brinciotti, 1994; Holmes, et al., 2007; Meador, et al., 2007; Stefovska, et al., 2008; Trimble, 1990; Viggedal, Hagberg, Laegreid, &

Aronsson, 1993). Thus, it is possible that the lower scores were attributable to the NAS medication, rather than the opioid-exposure per se.

Johnson and colleagues (H. L. Johnson, et al., 1987, 1990; H. L. Johnson & Rosen, 1982; Rosen & Johnson, 1982, 1985) found that methadone-exposed infants (*n*=62) scored more poorly on the MDI than their non-exposed peers (*n*=32), when assessed at six months of age. While the differences did not reach statistical significance, this was reportedly due to large within-group variance. It was also reported that lower BSID scores were significantly associated with abnormal neurological signs for the methadone-exposed infants (H. L. Johnson & Rosen, 1982). Repeat testing at 12 and 18 months showed that, although mean scores were within the average range, methadone-exposed infants achieved significantly lower scores on the MDI compared with the non-exposed infants. Additionally, there was a higher rate of recurring otitis media in the methadone-exposed infants, which may have been associated with lower MDI scores through deficits in auditory processing and subsequent learning and communication difficulties (Rosen & Johnson, 1982, 1985).

Van Baar et al. found that MDI scores of 24 and 30 month olds were significantly lower for infants prenatally exposed to heroin, methadone and cocaine (*n*=35), when compared with a group of non-exposed children (*n*=37). The authors suggested that the opioid-exposed children may have had difficulty with language comprehension and expression at these assessments, and indicated that home environment and social factors may have contributed to language difficulties, although these variables were not adjusted for in analyses. Additionally, as mentioned, 60% of opioid-exposed infants were also prenatally exposed to cocaine, which may have contributed to their poorer cognitive outcome (van Baar, 1990; van Baar, Fleury, & Ultee, 1989; van Baar, et al., 1994).

Hunt and colleagues (2008) reported that MDI scores of infants prenatally exposed to methadone (*n*=79) were significantly lower than non-exposed infants (*n*=61) at 18 months of age. However, mean scores for both groups of infants were in the normal range of development, and potentially important covariates such as gestational age, maternal use of other substances, treatment for NAS, or other health and social factors were not included in analyses.

The only previous study to assess the effect of prenatal-exposure to buprenorphine on MDI scores was that of Salo et al. (2009) who reported that, at three years of age, children prenatally exposed to buprenorphine (*n*=21) achieved significantly poorer scores on the Cognitive, Language and Social-Emotional Scales of the BSID-III, compared with non-exposed children (*n*=13). However, after adjusting for covariates (including gestational age, maternal age, SES and number of foster placements), only the Language Scale scores remained significantly associated with buprenorphine exposure (Salo, et al., 2009). The authors noted that over 40% of the buprenorphine-exposed infants were also exposed to other illicit substances, including benzodiazepines and amphetamines. As mentioned above, benzodiazepines are known to adversely affect cognitive performance (Viggedal, et al., 1993), thus exposure to other substances may have contributed to the infants' poorer cognitive outcome.

In the present study, overall there was a significant 6.7 point decrease in mean MDI scores over the course of the two assessments [12-month MDI: $M\pm SD$ = 100.46±1.14, 24-month MDI: $M\pm SD$ = 93.79±1.70; $t(71)$=3.80, $p<.001$]. When examining the mean scores of individual groups of infants, the mean MDI score of the control group fell by approximately four points, while the mean MDI score for the MM and BM groups fell by approximately eight points each. Similar to the present study, research by Chasnoff et al. (1982; 1984) showed a decline in mean MDI scores, between 12 and 24 months of age, for both methadone-exposed and non-exposed children, a finding which they attributed to low levels of SES and maternal education. The finding that mean MDI scores

declined with age is consistent with the results of Wilson (1989), who reported that MDI scores of

infants prenatally exposed to heroin, methadone and a non-exposed comparison group declined

across 9, 18 and 24 months. According to the authors, the level of disadvantage experienced by

the study population, particularly the poor home environments of the drug-exposed children, may

have contributed to the decline in scores (Wilson, 1989). The decline in MDI scores observed in

the present study cannot be attributed to poor home environment. Whilst home environment

appears to be a strong predictor of infant cognitive development (see Tables 6.2 and 6.5), mean

scores on the Total HOME scale for infants in the current study were generally high (see Table

3.11). The present study used HOME scores that were collected concurrently with the BSID-II

scores to predict cognitive developmental outcome, whilst Lifchitz, Wilson and colleagues

collected HOME scores at 36 months of age, not at the time of assessment with the MDI (Lifschitz,

et al., 1985; Wilson, 1989). Further, whilst this research group found that HOME scores were a

strong predictor of McCarthy General Cognitive Index scores at a mean age of three years and five

months (Lifschitz, et al., 1985), HOME scores were not examined in relation to the earlier tests of

cognitive development using the BSID; thus it is difficult to draw any firm conclusions about the

relationship between home environment and the MDI scores in Wilson's study (Wilson, 1989).

A study of infants prenatally exposed to cocaine (n=265), alcohol, tobacco and/or marijuana

(n=66), and a non-exposed control group (n=129), found that the infants prenatally exposed to

cocaine scored significantly lower than the other two groups on the MDI at 3, 6, and 12-months of

age (Mayes, Cicchetti, Acharyya, & Zhang, 2003). However, while the infants prenatally exposed

to cocaine continued to obtain the lowest scores at subsequent follow-up assessments, MDI at 24

to 36 months, did not differ significantly between the three groups. Results of this study also

showed that the mean scores of all infants declined between three and 36 months of age, with

the cocaine-exposed infants showing a greater decrease in scores over time compared with

infants in the other two groups. The authors commented that a decline in BSID scores was

common in high-risk samples and indicated that their study population was generally subject to poor environmental stability, high levels of parenting stress and extreme poverty. The authors suggested that the emphasis on language skills in the latter assessments may have contributed to the decline in scores for a high-risk population of children (Mayes, et al., 2003). However, again, the quality of the home environment was neither specifically measured, nor adjusted for in analyses, and parenting stress did not contribute significantly to any of the models.

Similarly, a study examining the development of cocaine-exposed infants (*n*=113) and non-exposed infants (*n*=90), found that scores on the BSID declined between six and 24 months of age for both groups of children (Frank et al., 2002). This research found that decline in MDI scores was greater for children residing with their biological mother or in the care of relatives than for children in non-relative foster care (Frank, et al., 2002). Only four infants in the present study (two in each of the BM and control groups) were cared for by relatives or were in non-relative foster care (see Chapter 2), thus subgroup analyses were not possible.

The significant decline in MDI scores observed in the present study may be attributable to prenatal benzodiazepine exposure. Examination of scores for infants whose mothers self-reported use of benzodiazepines in pregnancy (*n*=28; 4 controls, 12 each for MM and BM) showed a significant 14.5 drop in mean MDI scores across the two assessments [12-month MDI: $M \pm SD$ = 101.13±1.70, 24-month MDI: $M \pm SD$ = 86.61±2.83; $t(22)$=5.30, p <.0001]. In a sample of Swedish infants, Viggedal et al. (1993) found that infants prenatally exposed to therapeutic doses of benzodiazepines (*n*=17) achieved consistently lower scores on the General Developmental Quotient of the Griffiths' Mental Developmental Scale than a non-exposed group of infants (*n*=29) when tested at five, 10 and 18 months of age. Mean scores of infants prenatally-exposed to benzodiazepines were significantly lower than the non-exposed infants at 10 and 18 months of age. Infants exposed to benzodiazepines displayed deficits in personal-social behaviour, hand-eye

coordination and performance, along with deviations from normal activity and attention levels (Viggedal, et al., 1993).

A high proportion of children in the current study scored below the average range for the 24-month MDI. Table 6.1 shows that a greater proportion of infants in the BM group scored below the average range, compared with infants in the MM and control groups. The proportion of infants in the current study with scores below average (30% of the total sample) is twice that observed in the BSID-II normative sample (12.6%), and is also greater than that expected in a normal distribution, where approximately 16% of children would be expected to score below the average range (Bayley, 1993). The norms for the BSID-II were developed using a sample of 1700 infants from the United States, and did not include infants who were premature, those with a disability, or from other at-risk populations. Subsequently the norms reflect a North American non-clinical population in terms of race, ethnicity, gender and parental education levels (Bayley, 1993). In the present study, the non-exposed control group was selected based on socioeconomic status, therefore these differences from the norming sample are not unexpected, and cultural and social factors may also have contributed to the proportion of infants in the current study scoring below 'normal limits' on the MDI. Additionally, there are a large number of items in the 24-month MDI assessment related to expressive and receptive language acquisition, language comprehension, and vocabulary (e.g. naming and recognising pictures and objects, attending to a story). Maternal language and literacy levels are predictive of vocabulary production in infants from low-income families (Pan, Rowe, Singer, & Snow, 2005). While this study did not formally assess maternal literacy or language capabilities, many infants were from low-income families with low parental educational achievement (see Table 3.6). In the current study, a small number of women had difficulty with reading and writing to such an extent that they required help completing the questionnaires.

Psychomotor Developmental Index

In the current study, infants prenatally exposed to methadone achieved the lowest mean score on the 12-month PDI, approximately four points lower than that of infants prenatally exposed to buprenorphine and the non-exposed control group (see Table 6.1). When head circumference (HC) at birth was included in the analyses, larger HC at birth remained significantly associated with higher PDI scores at 12 months of age, but PDI scores remained unrelated to group status. At 24 months of age, mean scores on the PDI did not differ significantly between infants in the BM and MM groups. The mean score of the control group was approximately three points higher than those of the opiate exposed groups, although this difference in scores was not significant, and the effect size of the difference was small. When prenatal exposure to benzodiazepines, perceived maternal social support at four months of age, and current home environment were included in the analyses, prenatal exposure to benzodiazepines remained significantly associated with lower PDI scores, and better home environment remained significantly associated with better psychomotor development at 24-months of age.

Results of the current study are consistent with much of the previous research which has found that while infants prenatally exposed to methadone often experience delays in psychomotor development compared with non-exposed infants, mean scores tend to fall within the average range (Hans, 1989; H. L. Johnson & Rosen, 1982; Messinger, et al., 2004; Rosen & Johnson, 1982; Wilson, et al., 1981). Johnson and Rosen (H. L. Johnson & Rosen, 1982; Rosen & Johnson, 1982, 1985) reported that infants prenatally exposed to methadone (*n*=62) achieved lower scores on the PDI at six months of age compared with their non-exposed peers (*n*=32). As reported above, the differences did not reach statistical significance, reportedly due to large within-group variance. For the methadone-exposed infants only, low BSID scores were significantly associated with abnormal neurological signs (H. L. Johnson & Rosen, 1982). This cohort of children was re-assessed at 12, 18 and 24 months of age with the methadone-exposed children scoring

significantly lower on the PDI than the non-exposed infants. Again, all mean scores were within the average range (Rosen & Johnson, 1982).

Wilson and colleagues reported a significant delay in psychomotor development for 39 infants prenatally exposed to methadone, compared with 57 non-exposed infants, when assessed at nine-months of age. Specifically, the authors reported that infants prenatally-exposed to methadone demonstrated poorer fine-motor control (Wilson, et al., 1981). While no explanation for this was provided by the authors, it is possible that other social or genetic differences between the groups, such as maternal-infant interaction or race, may have influenced these results. Sleep disturbances and bouts of excessive crying were reported to be significantly more frequent in the methadone-exposed group than for the non-exposed infants (Wilson, et al., 1981). In the current study there was no difference in sleeping problems noted between groups (see Table 3.6). As mentioned above, serotonin assists in regulating the sleep/wake cycle and is important for coordination of sensory and motor responses. Animal studies have shown that prenatal exposure to methadone has been associated with increased levels of serotonin in the brain, thus the difficulties with fine motor control observed in the methadone-exposed infants in Wilson et al.'s study may be associated with increased serotonin levels in the brains of these infants (Konijnenberg & Melinder, 2011; Robinson, et al., 1997).

Similarly, Hans examined the psychomotor development of two-year-old children prenatally exposed to methadone (*n*=30) and compared it with the development of a group of non-exposed children (*n*=44). Groups were similar in terms of maternal IQ, years of education, single parent status, race and SES. Whilst mean scores fell within the average range, infants exposed to methadone had significantly lower PDI scores than non-exposed children, equating to a developmental delay of approximately two months (Hans, 1989).

More recently, Messinger et al. (2004) have described the psychomotor development of a large sample of toddlers (*n*=1227). They reported that opioid exposure was associated with significantly lower PDI mean scores at two and three years of age. Opioid-exposed children (*n*=98) also scored approximately four PDI points below non-opioid exposed children (*n*=1129). However, when analyses were adjusted for data collection site, infant age at testing, ethnicity, birth weight, infants' home environment, and maternal care, no significant effect of opioid exposure on psychomotor development remained. Similar to results of the present study, the research by Messinger et al. showed that higher HOME scores (indicating a more optimal home environment) were significantly associated with higher scores on the PDI (Messinger, et al., 2004).

Some research has found above average scores on the PDI for opioid-exposed infants. Very early research by Ramer and colleagues noted that while infants prenatally exposed to heroin and/or methadone (*n* =29) appeared to perform poorly on tasks requiring perceptual motor skills, mean PDI scores did not differ significantly from a non-exposed group of infants (*n* =10). All mean PDI scores were above average when assessed at one month of age (Lodge, et al., 1975; Ramer & Lodge, 1975). Similarly, van Baar et al. (1990; van Baar, Fleury, & Ultee, 1989) assessed the psychomotor development of 35 infants prenatally exposed to methadone and other substances (including heroin and cocaine) at six monthly intervals from six to 30 months of age. This study found that mean PDI scores were generally within the average to high-average range and did not differ significantly from a group of 37 non-exposed infants. Whilst the authors acknowledged that these results were inconsistent with previous research, no explanations were provided for the high psychomotor developmental scores obtained in their study (van Baar, Fleury, & Ultee, 1989). It may be that van Baar et al.'s sample differed from other research samples in terms of unmeasured cultural or social characteristics which may have influenced psychomotor development.

In the current study, benzodiazepine exposure remained significantly associated with lower PDI scores at 24 months of age. As discussed above, benzodiazepine exposure *in utero* has been linked to poorer developmental outcome in exposed infants. As well as deficits in cognitive development, distinctive hand and arm movements, not observed in non-exposed infants, have also been reported for infants prenatally exposed to benzodiazepines (Viggedal, et al., 1993).

Contrary to changes in mean MDI scores observed in the current study, mean PDI scores remained relatively stable across the 12- and 24-month assessments [t(71)= -0.50, p= .62]. Consistent with the pattern of results seen in relation to the 24-month MDI, a high proportion of children in the current study (29% of the total sample) scored below the average range for the 24-month PDI. Table 6.1 shows that, as with the MDI, a greater proportion of infants in the BM group scored below the average range, compared with infants in the MM and control groups. The proportion of infants in the current study with 24-month PDI scores below average was twice that observed in the BSID-II normative sample (14.8%) (Bayley, 1993). Additionally, whilst mean scores for all three groups of infants on the 12-month PDI were in the average range, scores were approximately half of one *SD* below the standardised mean of 100. At 24 months of age, all mean PDI scores were within the average range, however, mean scores of the BM and MM groups were again approximately half of one *SD* below the standardised mean. These results are similar to those of Johnson and Rosen (1982; Rosen & Johnson, 1985) who found that mean scores on the PDI were lower for infants prenatally exposed to methadone compared with a non-exposed group, when assessed at six, and 12 months of age. Additionally, a significantly greater proportion of methadone-exposed infants scored below the average range on the PDI, compared with infants in the non-exposed group (H. L. Johnson & Rosen, 1982; Rosen & Johnson, 1985).

To better understand the proportion of low PDI scores observed in the present study, it is useful to examine research involving other groups of at-risk infants who have been found to show

similar rates of low PDI scores. For example, Gibson et al. (1998) found that the mean 12-month

PDI scores of infants conceived via in-vitro fertilisation [(IVF), n=65, $M{\pm}SD$=90.4±14.8] and a group

of comparison infants (n=63, $M{\pm}SD$=89.5±15.5) were at the lower end of the average range, and

fell approximately two-thirds of one SD below the standardised mean (Gibson, et al., 1998). As

mentioned above, the BSID-II was standardised on a population of children in the United States,

whilst the participants in both the current study and in Gibson et al.'s study were drawn from

Australian populations. Gibson et al. posited that cultural factors may have accounted for the

lower PDI scores observed in their study, and it is possible that this may also be the reason for the

large proportion of infants in the current study scoring below 'normal limits' on the PDI.

Additionally, it was suggested that the lower scores observed in Gibson et al.'s study may have

been related to the re-standardised norms of the BSID-II, which the authors reported were not

used in earlier studies (Gibson, et al., 1998). The authors appear to be referring to a phenomenon

known as the 'Flynn effect', where average test scores are known to increase over time due to

changes in a population. Thus when a test is re-standardised, a decline in mean scores can be

expected (Gagnon & Nagle, 2000). It does not appear that the lower scores in the present study

can be attributed to the 'Flynn effect'. This is because the data for the standardisation of the

BSID-II was collected in 1988 (Pearson Education, 2008), therefore it would be expected that

mean scores in the present sample might be inflated when compared with the norming sample.

Gibson and colleagues also suggested that the lower scores in their sample may have been due to

the large number of items in the 12-month item-set for the PDI that assess a child's ability to

stand and walk independently (Gibson, et al., 1998). It is possible that this may account for the

lower 12-month PDI scores observed in the present study; however, it is unlikely that this is the

reason behind the lower PDI scores observed at 24 months. In research mentioned above (Frank,

et al., 2002), PDI scores of cocaine-exposed and non-exposed children, assessed at six, 12 and 24

months of age were significantly associated with early child-focussed developmental intervention.

Children who received any form of early intervention (including parent-child groups, home health services, and clinical services such as occupational or speech therapy), regardless of cocaine exposure status, showed an increase in PDI scores, whilst children not receiving any intervention services showed a significant decline in PDI scores across the assessment periods (Frank, et al., 2002). While anecdotally it was found that some families in the current study had accessed parenting support, health, and other clinical services, children's involvement with early intervention services was not formally assessed. Thus, it was not possible to examine the impact of this sort of intervention on developmental outcomes in the current study.

Behavior Rating Scale

Very few previous studies have examined behaviour, using the BRS, in opioid-exposed infants. In the present study, mean scores on the BRS did not differ significantly between the three groups of infants at 12 months of age. The mean score of the BM group was approximately three points higher than for infants in the other two groups, although this difference was not significant and the effect size of the difference was small. Male infants were more than three times as likely as female infants to obtain a behaviour score below the average range (p=.07). When infant gender, perceived maternal social support at four months of age, and current home environment were included in the analyses, male gender remained significantly associated with lower BRS scores, and a more optimal home environment remained significantly associated with higher BRS scores at 12-months of age (see Table 6.4).

Consistent with the assessment at 12 months of age, behaviour scores were similar across the three groups of infants at 24 months of age. When perceived maternal social support at four months of age and current home environment were included in the analyses, 24-month home environment remained the only significantly predictor of 24-month behaviour score, with a more optimal home environment associated with higher BRS scores at 24-months of age (see Table

6.7). Contrary to the finding at 12 months, there was no effect of infant gender on behaviour at two years of age. There was a significant 14 point decline in mean BRS scores over the two assessments [$t(59)=10.42$, $p<.0001$]. This decrease in the scores may reflect normal developmental changes in toddler behaviour, where two year old children may have been starting to assert their independence and were thus becoming more difficult to assess, and less compliant than 12 month olds. Alternatively, the change in scores may be due to other developmental problems, not yet diagnosed, such as ADHD or autism, beginning to emerge.

The findings of the current study are similar to those of Frank and colleagues (2002) who found no significant differences in Infant Behaviour Record scores (IBR, the precursor scale to the BRS) between cocaine-exposed infants and non-exposed infants when assessed at six and 24 months of age. However, contrary to results of the current study, Frank et al. found no significant decline in IBR scores across assessments for either group of children (Frank, et al., 2002).

More recently, Messinger et al. (2004) reported that, in univariable analyses, mean 24-month BRS scores for opioid exposed children were significantly lower than for non-opioid exposed children. However, in multivariable analyses overall performance on the BRS was not associated with prenatal exposure to opioids. Mean BRS scores of opioid-exposed infants did not differ significantly from non-exposed infants at 12 or 36 months of age. As with the current study, Messinger et al. (2004) reported that BRS scores decreased between 12 and 24 months of age. However, unlike the present study, the decline in scores for the Messinger sample was not significant. Additionally, mean scores for each group actually significantly rose after the 24 month assessment, although substance exposure was not associated with this increase in scores. Similar to the present study, Messinger and colleagues found that higher scores on the HOME scale were significantly associated with higher infant behaviour scores (Messinger, et al., 2004).

In contrast to results found in the current research, Hans (1989) reported that methadone-exposed infants scored significantly higher (indicating poorer functioning) on the tension, gross motor coordination and fine motor coordination items of the Infant Behaviour Record (IBR) than non-exposed infants at 24 months of age. Although it was noted that mean scores for all items were within the average range. When children from low SES families were examined separately, methadone-exposed infants from low SES backgrounds scored more poorly on the IBR items than non-exposed infants. The author concluded that prenatal exposure to methadone may increase susceptibility to the effects of a disadvantaged environment (Hans, 1989).

There are a number of possible explanations for the results obtained in the present study. As discussed above, prenatal exposure to opioids may be associated with disturbances to selective neurotransmitter systems, which may in turn influence attention, memory and other cognitive functioning, along with motor control in exposed infants and children. Secondly, prenatal exposure to benzodiazepines has been shown to be associated with deviations in brain development and subsequent deficits in cognitive and motor performance which may not become evident until later infancy (Viggedal, et al., 1993). Thirdly, maternal literacy and language capabilities, along with cultural factors specific to this population of children, may have contributed to the large proportion of infants who scored below the average range on the MDI and PDI. Finally, it is evident from the results of the present study that the quality of the home environment is arguably the most important influence on a child's cognitive, motor and behavioural development, over and above prenatal substance exposure. This result is consistent with previous research which has demonstrated the considerable effect of socioenvironmental factors on children's development (Lifschitz, et al., 1985; Messinger, et al., 2004; Tong, et al., 2006; Wilson, 1989).

CHAPTER 7

Infant Temperament

This chapter describes the temperament of infants at four, 12 and 24 months of age, as measured with the Short Temperament Scale for Infants (STSI) and the Short Temperament Scale for Toddlers (STST) (Prior, et al., 1989; Sanson, et al., 1987). First, temperament factor scores at four, 12 and 24 months of age were examined. Second, relationships between potential confounding variables and the composite Easy/Difficult Scale (EDS) scores of the Temperament Scales were evaluated, and differences in EDS scores between groups were then analysed adjusting for significant confounding variables. Third, change in EDS scores over time was examined across the three groups of infants.

This chapter addresses the following hypotheses:

Hypothesis 9:

Composite Easy/Difficult Scale (EDS) scores of infants prenatally exposed to buprenorphine will not differ significantly from a non-exposed control group when assessed at four, 12 and 24 months of age.

Hypothesis 10:

Composite EDS scores of infants prenatally exposed to methadone will be significantly higher, indicating more difficult temperament, than those of infants prenatally exposed to buprenorphine and a non-exposed control group of infants when assessed at four, 12 and 24 months of age.

Hypothesis 11:

Change in composite EDS scores over time will not vary significantly between children prenatally exposed to buprenorphine, methadone, or in a non-exposed control group.

Statistical analyses

Analyses were conducted according to the methods described in Chapter 2, section 2.7, and previously outlined in the statistical analyses section of Chapter 4.

Briefly, a series of simple linear regression analyses and ANOVAs were conducted to examine the contribution of independent variables to the EDS scores at four, 12 and 24 months of age. Standard multiple regression analyses were then conducted to examine the contribution of each independent variable to the individual EDS scores, whilst adjusting for the effect of the other variables in the model. Finally, a split-plot ANOVA was undertaken to examine whether EDS scores changed over time, and whether change in EDS scores varied between infants in each of the three groups. Because the STSI and the STST differ slightly in their content and factor structure (Pedlow, Sanson, Prior, & Oberklaid, 1993), interpreting change in mean EDS scores between the four month follow-up assessment and the other two follow-up assessments, at 12 and 24 months, may be problematic. Therefore, in order to directly compare the scores at each time point, the raw EDS scores were converted to z-scores for use in the split-plot ANOVA.

7.1 Infant Temperament at four months of age

Temperament scores were collected successfully from 86/87 (99%) of participating infants at the four month follow-up assessment. The mother of one male BM infant did not complete the Short Temperament Scale for Infants, as he was not in her care at the time of this assessment.

Table 7.1 shows that at four months of age there were no significant differences between the three groups of infants for any of the temperament factor scores: Approach factor [Kruskal-Wallis: χ^2 (2) = 0.46, *n* = 86, *p* = .80], Rhythmicity factor [Kruskal-Wallis: χ^2 (2) = 3.67, *n* = 86, *p* = .16], Cooperation/Manageability factor [F(2,83) = 0.75, *p* = .48, power 0.4 transformation],

Activity/Reactivity factor [$F(2,82) = 0.54$, $p = .58$], and Irritability factor [$F(2,82) = 0.03$, $p = .97$, square root transformation].

At four months of age mean Composite Easy/Difficult Scale (EDS) scores did not differ significantly between the three groups of infants [$F(2,83) = 0.16$, $p = .85$, square root transformation, $\eta^2 = .004$] (Table 7.1). Overall, EDS scores for 64% of all infants fell within the 'Average' temperament range, 30% of the sample (nine controls, seven BM, ten MM) scored within the 'Easy' temperament range ($\leq$ 1SD below the standardised mean of 2.50), while 6% (three controls, two MM) scored in the 'Difficult' temperament range ($\geq$ 1SD above the standardised mean). There was no significant difference in temperament rating between the three groups of infants (Fisher's exact test $p = .21$), and no difference between boys and girls (Fisher's exact test $p = .94$).

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

Lower EDS scores (indicating easier temperament) at four months of age were significantly associated with (1) higher maternal postnatal Global Attachment Scores (indicating better maternal-infant attachment) at four months of age [$\beta = -.48$, $t(83) = -5.02$, $p < .001$], (2) lower maternal psychological distress at four months of age [$\beta = .41$, $t(84) = 4.09$, $p < .001$, square root transformation], and (3) better perceived maternal social support at four months of age [$\beta = -.27$, $t(84) = -2.52$, $p < .05$, square root transformation].

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

Variables entered into the model were 4-month EDS scores as the dependent variable, with maternal postnatal Global Attachment Score at four months, maternal psychological distress (GHQ Total Score) at four months, perceived maternal social support (ISSI-SF Total Score) at four months of age and group (control group as the reference) as the predictor variables. Table 7.2

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shows that, after adjustment for other covariates, Global Attachment Score remained a significant predictor of infant EDS scores at four months of age ($p < .001$) and provided the largest unique contribution to the variance in the model. GHQ Total Score at four months of age also remained significantly associated with infant EDS scores at four months of age ($p < .01$), and provided the next largest contribution to the variance in the model. Overall, the model explained 32% of the variance in EDS scores at four months of age and was significant at $p < .0001$. After adjusting for covariates, ISSI-SF Total Score did not provide a significant contribution to the model. In addition, group was not significantly associated with EDS scores at four months of age [$F(2,79) = 0.47$, $p =.62$], after adjusting for covariates, indicating that prenatal exposure to buprenorphine or methadone did not influence infant temperament at four months of age.

7.1.3 Summary of Infant Temperament at four months of age

Easy/Difficult Scale (EDS) scores at four months of age did not differ significantly between the three groups of infants, after adjusting for maternal postnatal attachment, maternal psychological distress, and perceived maternal social support. Maternal postnatal attachment remained a significant predictor of EDS scores at four months of age ($p < .001$), with better maternal-infant attachment related to easier infant temperament. Lower maternal psychological distress also remained significantly associated with easier infant temperament at four months of age ($p < .01$).

7.2 Infant Temperament at 12 months of age

Temperament scores were collected from all ($n = 83$) participating infants at the twelve month follow-up assessment.

Table 7.3 shows that at 12 months of age there were no significant differences across the three groups of infants on any of the temperament factor scores: Approach/ Adaptability factor [Kruskal-Wallis: $\chi^2 (2) =0.90$, $n=83$, $p=.64$], Reactivity factor [$F(2,79)=1.52$, $p=.23$], Persistence

factor [$F(2,79) = 1.46$, $p = .24$], Cooperation/Manageability factor [$F(2,80) = 0.37$, $p = .69$], Distractibility factor [$F(2,80) = 1.33$, $p = .27$], and Rhythmicity factor [$F(2,79) = 0.71$, $p = .50$].

One-way ANOVA showed that, at 12 months of age, mean EDS scores were very similar across the three groups of infants (Table 7.3). With a small effect size of $\eta^2 = .01$, this difference did not reach statistical significance [$F(2,80) = 0.25$, $p = .78$, log transformation]. Overall, 77% of infants scored within the 'Average' temperament range on the 12-month EDS scores, 11% (three controls, four BM, two MM) scored within the 'Easy' temperament range ($\leq$ 1SD below the standardised mean of 3.46), while 12% (four controls, four BM, two MM) scored in the 'Difficult' temperament range ($\geq$ 1SD above the standardised mean). There was no significant difference in temperament rating between the three groups of infants (Fisher's exact test $p = .94$), and no difference between boys and girls (Fisher's exact test $p = .42$).

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

Lower EDS scores (indicating easier temperament) at 12 months of age were significantly associated with higher maternal postnatal attachment scores (indicating better maternal-infant attachment) at four months of age [$\beta = -.32$, $t(80) = -3.00$, $p < .01$]. Although there was an interesting suggestion of a relationship between higher 12-month EDS scores (indicating more difficult temperament) and 1) higher scores on the GHQ at four months of age (indicating higher levels of maternal psychological distress), and 2) higher scores on the Parenting Stress Index (suggesting higher levels of parenting stress) at 12 months of age, neither of these relationships reached conventional levels of statistical significance [GHQ: $\beta = -.21$, $t(81) = -1.91$, $p = .06$, inverse transformation; PSI: $\beta = .21$, $t(75) = 1.85$, $p = .07$, log transformation].

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

Variables entered into the model were 12-month EDS score as the dependent variable, with maternal postnatal Global Attachment Score at four months and group (control group as the reference) as the predictor variables. Table 7.4 shows that, after adjustment for other covariates, Global Attachment Score remained a significant predictor of infant EDS scores at 12 months of age ($p < .01$) and provided the largest unique contribution to the variance in the model. After adjusting for covariates, group status was not significantly associated with EDS scores at 12 months of age [$F(2,78) = 0.16$, $p = .85$]. PSI Parent Domain Total score at 12 months of age and General Health Questionnaire (GHQ) Total score at four months were not included in the multivariable analyses because with limited study numbers, the use of too many covariates can be problematic. There was also a large amount of missing data for the PSI Parent Domain Total score and its inclusion in the multiple regression analysis further reduced the available sample size. However, when GHQ Total score at four months replaced the Global Attachment Score in the model, the overall results remained similar and it did not make a significant contribution to the model (results not shown).

7.2.3 Summary of Infant Temperament at 12 months of age

Twelve month EDS scores did not differ significantly between the three groups of infants, after adjusting for maternal postnatal attachment. Global Attachment Score at four months of age remained a significant predictor of infant EDS scores at 12 months of age ($p < .01$), with better maternal-infant attachment at four months of age associated with easier infant temperament at 12-months of age.

7.3 Temperament at 24 months of age

Temperament scores were collected from 71/ 73 (97%) participating infants at the twenty-four month follow-up assessment. Two families (one each in the BM and MM groups) did not return a completed questionnaire at this assessment.

Table 7.5 shows that at 24 months of age there were no significant differences between the three groups of infants for any of the temperament factor scores: Approach/ Adaptability factor [$F(2,68)$ = 1.86, p = .16], Reactivity factor [$F(2,68)$ = 0.15, p = .86], Persistence factor [$F(2,68)$ = 1.57, p =.22], Cooperation/Manageability factor [Kruskal-Wallis: χ^2 (2) = 0.02, n = 71, p = .99], Distractibility factor [$F(2,68)$ = 1.44, p = .24], and Rhythmicity factor [$F(2,68)$ = 2.08, p = .13].

One-way ANOVA showed that, at 24 months of age, mean EDS scores did not differ significantly between the three groups of infants (Table 7.5) [$F(2,68)$ = 0.21, p = .81, square root transformation]. At 24 months of age, EDS scores of 75% of participating infants fell within the 'Average' temperament range, 6% of the sample (two controls, one each in the BM and MM groups) scored within the 'Easy' temperament range ($\leq$ 1SD below the standardised mean of 3.32), while 20% (eight controls, three each in the BM and MM groups) scored in the 'Difficult' temperament range ($\geq$ 1SD above the standardised mean). There was no significant difference in temperament rating between the three groups of infants (Fisher's exact test p = .75), and no difference between boys and girls (Fisher's exact test p = .76).

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

Lower EDS scores (indicating easier temperament) at 24 months of age were significantly associated with (1) higher maternal postnatal Global Attachment Scores (indicating better maternal-infant attachment) at four months of age [β = -.35, $t(68)$ = -3.06, p <.01], (2) better

perceived maternal social support at four months of age [Spearman's rho= -.33, *n* =71, *p* <.01], and (3) lower scores on the Parenting Stress Index (suggesting lower levels of parenting stress) at 24 months of age [β = .35, *t*(59) = 2.88, *p* <.01]. There was an interesting suggestion of a relationship between higher 24-month EDS scores (indicating more difficult temperament) and higher scores on the GHQ (indicating higher levels of maternal psychological distress) at four months of age, and lower maternal educational attainment, however, neither of these associations reached conventional levels of statistical significance [GHQ: Spearman's rho = .23, *n* = 71, *p* = .06; maternal education: *F*(1,69) = 3.54, *p* = .06].

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

Variables entered into the model were 24-month EDS score as the dependent variable (square transformation), with maternal postnatal Global Attachment Score at four months, perceived maternal social support (ISSI-SF Total Score) at four months of age, and group (control group as the reference) as the predictor variables. Parenting Stress Index Score at 24 months of age was not included in the multivariable analysis because it was significantly correlated with ISSI-SF Total Score at four months of age [Pearson correlation coefficient = -.67, n = 61, *p* < .0001] and, as there was a large amount of missing data, its inclusion in the multiple regression considerably reduced the available sample size. Table 7.6 shows that, after adjustment for other covariates, Global Attachment Score remained a significant predictor of infant EDS scores at 24 months of age (*p* < .05) and provided the largest unique contribution to the variance in the model. After adjusting for covariates, neither ISSI-SF Total Score, nor group status [*F*(2,65) = 0.21, *p* = .81] contributed significantly to the model.

7.3.3 Summary of Infant Temperament at 24 months of age

Twenty-four month EDS scores did not differ significantly between the three groups of infants after adjusting for maternal postnatal attachment and perceived maternal social support at four months of age. After adjusting for covariates, better maternal postnatal attachment at four months of age remained a significant predictor of lower infant EDS scores (indicating easier temperament) at 24 months of age ($p<.05$).

7.4 Longitudinal analyses of Easy/Difficult Scale Scores

Figure 7.1 shows the mean EDS (raw) scores of each group at each of the three follow-up assessments. As mentioned earlier, the STSI and the STST differ in their content and factor structure (Pedlow, et al., 1993). Because of this, it is difficult to directly compare the raw EDS scores for the four-month assessment with the 12- and 24-month EDS scores. In order to examine whether there was any variation in change in temperament over the three assessments, between the three groups of infants, the raw EDS scores were converted to z-scores. A z-score is a standardised variable with a mean equal to zero, and a standard deviation equal to one (A. L. Edwards, 1979). To convert the raw data to z-scores, the mean of the observed EDS scores was taken away from the EDS score of each infant, and divided by the standard deviation of the observed scores. Figure 7.2 shows the mean EDS z-scores of each group at each of the three follow-up assessments.

A split-plot ANOVA was conducted with the EDS z-scores as the dependent variable, group entered as the between-subjects factor, and time (4, 12 and 24 months) entered as the within-subjects factor. Global Attachment score at four months of age was entered as a covariate. Preliminary checks were conducted to ensure that there was no violation of the assumptions of normality, linearity, homogeneity of variances, and homogeneity of regression slopes.

The ANOVA showed that the main effect for time was not significant [$F_{(2,145)}$ = 0.09, p = .91]. This result indicates that EDS scores did not change significantly over the three follow-up assessments. The ANOVA showed no significant main effect for group [$F_{(2,82)}$ = 0.50, p = .61], or Global Attachment score [$F_{(1,82)}$ = 0.04, p = .84]. Additionally, the time × group interaction did not reach statistical significance [$F_{(4,145)}$ = 0.27, p = .90], indicating that changes in EDS scores over the three follow-up assessments did not vary significantly between the three groups of infants. The effect sizes for all variables were small (η^2 < .01).

7.4.1 Summary of temperament longitudinal analyses

Results of the split-plot ANOVA supported the hypothesis that change in temperament scores over time would not vary significantly between infants prenatally exposed to buprenorphine, methadone or the non-exposed control group of infants. The interaction between group status and time was not significant, indicating that change in EDS scores over the three follow-up assessments did not differ significantly between the three groups of infants.

7.5 Discussion

This chapter compared the temperament of infants exposed to methadone or buprenorphine in pregnancy with that of a group of non-exposed infants. The key findings were that temperament, as measured by the Easy/Difficult Scale scores (EDS) on the Short Temperament Scale for Infants at four months of age, and the Short Temperament Scale for Toddlers at 12 and 24 months of age, did not differ significantly between infants prenatally exposed to buprenorphine, methadone, or a non-exposed control group. There was no change in this relationship after adjustment for covariates. As hypothesised, change in EDS over time did not vary significantly between the three groups of infants. These findings are important in terms of providing support for the ongoing use of both methadone and buprenorphine in pregnancy.

As described in Chapters 4 and 6, animal studies have shown that prenatal exposure to opioids can result in disturbance to the normal development of neurotransmitter systems in the developing infant. In terms of how this may affect temperament in exposed infants and children, research has shown that serotonin influences latent inhibition, behavioural organisation, is involved in the coordination of sensory responses, and is important in regulating sleep/wake cycles (Herlenius & Lagercrantz, 2004; Konijnenberg & Melinder, 2011). In animals, prenatal exposure to methadone has been shown to influence the serotonin transport system in the cortex and hippocampus, and increases in serotonin have been observed in the parietal cortex, compared with non-exposed controls (Konijnenberg & Melinder, 2011; Robinson, et al., 1997). In addition, opioids are known to disrupt circadian rhythms and alter the response to stress (Pechnick, 1993). Previous research has suggested that opioids may act indirectly upon the cholinergic system, which in the CNS is responsible for regulation of memory, learning, and attention (Everitt & Robbins, 1997). Specifically, opioid-exposure has the effect of delaying and disrupting cholinergic development in the striatum (Robinson, 2000, 2002; Wu, et al., 2001), which is involved in the regulation of attention and inhibitory control (Herrero, et al., 2002; Roberts, et al., 2004). Wu and colleagues (2001) found that exposure to 9 mg/kg/day methadone or 1.5 mg/kg/day buprenorphine (delivered prenatally, postnatally, or both) reduced striatal nerve growth factor (NGF) content in 10-day-old rat pups. NGF is thought to be responsible for delays in cholinergic phenotype expression, which may subsequently disrupt the development of cholinergic neurons. These mechanisms may be responsible for behavioural difficulties, such as high rates of distractibility and poor inhibition, observed in some opioid-exposed human infants (Tempel, et al., 1995; Tiong & Olley, 1988; Wu, et al., 2001).

In the current study, mean temperament factor scores for infants prenatally exposed to methadone, buprenorphine and a non-exposed control group, at 4, 12, and 24 months of age, were all within the average range, when compared with Australian general population norms

(Oberklaid, et al., 1986; Sanson, et al., 1985). Furthermore, Easy/Difficult Scale (EDS) scores at each assessment were within the average range for all groups of infants. EDS scores did not differ significantly between the control group and the two substance-exposed groups at any of the three assessments. Higher maternal postnatal Global Attachment Scores at four months of age, indicating better maternal-infant attachment, were significantly associated with lower EDS scores, indicating easier temperament, at each assessment. In addition, lower GHQ Total Scores at four months of age, indicating lower self-reported maternal psychological distress, were significantly associated with easier temperament at four months of age. There were no differences in the proportion of infants in each of the three groups with maternal reported temperament in either the 'Easy' or 'Difficult' ranges at any of the three assessments.

As reported in Chapter 1, only a small number of previous studies have specifically examined the construct of temperament in substance-exposed infants and children (van Baar, Fleury, & Ultee, 1989; Weiss, et al., 2007). Early studies of self-regulatory behaviour have used the Brazelton Neonatal Behavioural Assessment Scale (NBAS), which assesses similar constructs to those examined in temperament scales. For example, the NBAS has shown to be moderately to strongly correlated with scores on the Carey Infant Temperament Questionnaire (Sostek & Anders, 1977). Studies using the NBAS have generally found that infants prenatally exposed to methadone exhibit poorer neurological functioning than non-exposed infants. Lodge and colleagues (1975) found that when assessed during the first week of life, infants prenatally exposed to methadone and/or heroin (n = 27) were significantly less alert, had significantly poorer visual orientation and greater levels of hypertonicity than non-exposed infants (n=10). Additionally, the opioid-exposed infants showed increased levels of irritability, activity and poor state lability when compared with the non-exposed group. The authors reported that a large proportion of the opioid-exposed infants required pharmacological treatment for NAS symptoms (Lodge, et al., 1975). Chasnoff et al. (1982; 1984) found that infants prenatally exposed to methadone (n=39) performed

significantly more poorly on NBAS tasks of orientation and motor maturity, than infants in poly-drug exposed infants (combinations of benzodiazepines, marijuana and other illicit substances, n=19) and a non-exposed comparison group (n=27) when assessed at two days of age. Research by Jeremy and Hans (1985) showed that, when assessed during the first week of life on the NBAS, infants prenatally exposed to methadone (n=29) had significantly higher levels of irritability, activity, tremulousness, hypertonicity, and significantly lower levels of motor maturity than non-exposed infants (n=37). Additionally, the methadone-exposed infants were less 'cuddly', had higher levels of arousal, were more labile, less able to self-soothe, and displayed more hand-sucking than the non-exposed infants (Jeremy & Hans, 1985). The authors suggested that the difficult behaviours displayed by the methadone-exposed infants may place them at risk of poor attachment relationships. Reportedly, at one month of age, the methadone-exposed group continued to have significantly increased muscle tone, although other behaviours did not differ significantly between the two groups of infants (Jeremy & Hans, 1985). Finally, van Baar et al. (1989) found that whilst NBAS scores of infants prenatally exposed to combinations of methadone, heroin and cocaine (n=28) were poorer than a non-exposed control group of infants (n=37), at both 40 and 44 weeks post-conception, these differences were not statistically significant. Follow-up at three months of age indicated that the opioid-exposed infants were significantly more active than their non-exposed peers. This difference was not evident at six months of age, and it was suggested that the early activity levels may be associated with sub-acute symptoms of NAS (van Baar, Fleury, & Ultee, 1989).

Three studies have used validated temperament questionnaires with populations of substance-exposed children. Weiss et al. (2007) found that mothers of six month old infants prenatally exposed to cocaine or opiates (n = 30) rated them as significantly more distractible and intense in their expressiveness on the Revised Infant Temperament Questionnaire, than mothers of infants not exposed to any substance (n = 90). However, after adjusting for covariates, only infant

distractibility remained significantly associated with prenatal substance exposure. The authors suggested that the higher levels of distractibility observed in prenatally exposed infants may be associated with poor regulation of the arousal and excitatory response (Weiss, et al., 2007). Van Baar et al. (1989) found no significant differences in caregiver-rated temperament scores on a Dutch version of the Infant Behaviour Questionnaire, between nine-month old infants prenatally exposed to combinations of methadone, heroin and cocaine (n=28), and a non-exposed control group of infants (n=37). According to the authors, the substance-exposed infants had a slightly longer duration of orientation toward a single object, suggesting improved concentration, when compared with the non-exposed infants. No other differences in temperament ratings were reported (van Baar, Fleury, & Ultee, 1989).

Quinlivan and Evans (2005) found that teenage mothers who were subject to domestic violence whilst pregnant (n=33) rated their six month old infants as significantly more irritable and more difficult, on the Short Temperament Scale for Infants, than mothers who were not subject to domestic violence (n=84). Additionally, after adjusting for covariates, infants whose mothers used illicit substances (primarily marijuana) during pregnancy were five times as likely as infants not exposed to an illicit substance, to be rated as having a difficult temperament, independent of maternal experience of domestic violence (Quinlivan & Evans, 2005). However, as only a subset of the overall sample reported use of illicit substances during pregnancy ($N = 31$), results from this multivariable analysis must be interpreted with caution.

Only one study has examined the self-regulatory behaviour of infants prenatally exposed to buprenorphine (Sarfi, et al., 2009). Researchers in Norway found no differences in sleep patterns, amount of day or night time wakefulness, or the number of episodes of day-time distress, between 35 three month old infants prenatally exposed to opioid-maintenance medication (buprenorphine, $n = 11$; methadone, $n = 24$), and a group of 36 non-exposed comparison infants

(Sarfi, et al., 2009). However, as results were not shown separately for infants prenatally exposed to buprenorphine or methadone, it is not possible to identify the specific effect of buprenorphine exposure on infant self-regulatory behaviour.

Considered together, results for the above studies suggest that infants who are exposed to substances *in utero* have a tendency to display neurobehavioural difficulties in the early weeks of life, compared with non-exposed infants. It is highly likely that the poorer self-regulation demonstrated by substance-exposed infants is associated with NAS (Finnegan, 1990). Indeed, the cluster of symptoms that comprise NAS has been equated to the 'difficult' temperament profile described by Thomas and Chess (Jeremy & Bernstein, 1984). Whilst some difficulties in temperament, such as high levels of distractibility and irritability, may persist at least until nine months of age, it appears that beyond the neonatal period, differences in temperament between substance-exposed and non-exposed infants are not as pronounced.

In the present study, mother-infant attachment, assessed at four months post-partum, remained significantly associated with caregiver ratings of infant temperament at each of the three follow-up assessments. Additionally, a concurrent measure of maternal psychological distress was significantly associated with infant temperament ratings at four months of age, but not at later assessments. Previous research has shown that concurrent depression may influence mothers' views of infant temperament and behaviour, with depressed mothers viewing their infants as more difficult to care for, and as having more behavioural problems than infants of non-depressed mothers (Edhborg, Seimyr, Lundh, & Widstrom, 2000; Najman et al., 2000; Whiffen & Gotlib, 1989). However, when concurrent measures are used, it is not easy to establish the direction of cause-and-effect relationships between variables which are significantly associated. For example, it is equally possible that mother's mental health influences infant temperament, and that infant temperament influences maternal mental health. Additionally, is difficult to

determine whether maternal mental health influences infant temperament, or whether poor mental health colours maternal perceptions of child temperament. We attempted to address these issues with a prospective longitudinal design.

As noted earlier, maternal psychological distress (GHQ Total score) at four months of age was significantly associated with caregiver ratings of child temperament at four months of age, after adjustment for covariates. Although there was a suggestion of a relationship between maternal psychological distress at four months and child temperament at 12 and 24 months, these univariable analyses did not reach conventional levels of statistical significance. Since maternal-infant attachment at four months of age remained a significant predictor of temperament at 4-, 12-, and 24-months of age, but maternal psychological distress was a significant predictor of temperament at only 4-months of age, this would suggest that maternal-infant attachment may be the more important predictor of child temperament. Given the findings of previous research, the possibility that maternal psychological distress mediates the apparent effect of maternal-infant attachment on child temperament, or shows common variance with maternal-infant attachment, cannot be discounted.

Independent observations of infant temperament by another rater may overcome this problem; however, examiner-rated questionnaires are limited in that they assess only situation-specific behaviour (Whiffen & Gotlib, 1989). In the current study, ratings of infant behaviour were assessed at the 12 and 24 month follow-up assessments, using the Behaviour Rating Scale (BRS) of the Bayley Scales of Infant Development - Second Edition (see Chapter 6). Correlations between the BRS and caregiver ratings of infant temperament on the STST were small (r = .06 to -.24), with only the relationship between the 24-month BRS and 24-month EDS score nearing conventional levels of statistical significance (r = -.24, p = .052).

In summary, whilst some studies indicate that prenatal exposure to opioids may influence infant temperament, it is possible that the presence of NAS symptoms confounds the measurement of underlying self-regulatory behaviour. Results of the current study suggest that assessment beyond the neonatal period, when the transient effects of substance exposure are less likely to influence outcomes, is important. Additionally, consideration must be given to the effect that maternal mental health may have on ratings of infant temperament. Results of the current study indicate that maternal-infant attachment and maternal psychological distress at four months of age are strong predictors of caregiver ratings of both current and future infant temperament, regardless of prenatal substance-exposure. These findings suggest that early psychological interventions, including cognitive behavioural and attachment-based therapies, designed to strengthen maternal mental health and support maternal-infant attachment, may enhance infant temperament outcomes.

CHAPTER 8

Conclusion and Recommendations

Rising drug abuse is a worldwide phenomenon (Bell & Lau, 1995), with recent research pointing to increases in the number of people entering drug-treatment programs, as well as escalations in rates of drug-related harm and death (Anderson, 2006; Degenhardt, Hall, Warner-Smith, & Lynskey, 2004). For example, the 2010 National Drug Strategy Household Survey (NDSHS (Australian Institute of Health and Welfare, 2011) found that the proportion of Australians reporting use of illicit substances within the previous 12 months had increased from 13.4% in 2007 to 14.7% in 2010 (Australian Institute of Health and Welfare, 2011). This is a substantial increase from that reported in the 1997 Australian National Survey of Mental Health and Well-Being, which found that 10.8% of Australians had reported recent use of an illicit substance (McBride, et al., 2009).

Research reports that a large proportion of the drug using population are women of childbearing age (Laken, et al., 1997), with the 2010 NDSHS reporting that recent illicit drug use was highest among young people aged 18-29 years, and recent heroin use most frequently reported by Australians aged 30-39 years (Australian Institute of Health and Welfare, 2011). This report found that overall, there was a statistically significant increase in recent illicit drug use by females from 11% in 2007 to 12.3% in 2010 (Australian Institute of Health and Welfare, 2011).

Prenatal exposure to illicit opioids increases the risk of poor obstetric outcomes, growth deficits, and developmental problems in exposed infants and children, when compared with their non-exposed peers (Adams, et al., 1989; Berlin, et al., 1998; Chang, et al., 1992; Kandall, et al., 1976; Laken, et al., 1997; Robins & Mills, 1993). Methadone is the current gold-standard treatment for

pregnant, opioid-dependent women, and while there are many benefits of methadone-maintenance during pregnancy, its use is associated with high rates of neonatal abstinence syndrome (NAS). Additionally, infants who are prenatally exposed to methadone may experience deficits in physical growth, as well as longer term developmental and behavioural difficulties, compared with non- exposed infants (Australian Drug Foundation, 2005b; Bernstein, et al., 1984; Chang, et al., 1992; Davis & Templer, 1988; Dunlop, et al., 2003; Finnegan & Kandall, 1997; R. E. Johnson, Jones, et al., 2003; Lejeune, et al., 2006; Lintzeris, et al., 2006; Marcus, et al., 1984; van Baar, Fleury, Soepatmi, et al., 1989; van Baar, et al., 1994; Wilson, 1989).

Whilst methadone appears to be an effective and acceptable treatment for opioid-dependence in pregnancy, buprenorphine is now increasingly being prescribed as a maintenance medication. This is because its partial agonist properties result in milder withdrawal effects, a longer duration of action, and an improved safety profile in comparison to methadone. There is a growing body of research to support the safety and efficacy of buprenorphine during pregnancy and the early neonatal period, however its use during pregnancy is still restricted in some countries, including Australia (Lintzeris, et al., 2006). This is because studies to date have been limited by small numbers, lack of comparison to existing treatments and control groups, retrospective designs, and short follow-up periods (Gordon, 2006; R. E. Johnson, Jones, et al., 2003; Jones, et al., 2005; Jones, et al., 2010; Kayemba-Kay's & Laclyde, 2003; Lacroix, et al., 2004; Lejeune, et al., 2006). Further, information regarding longer term developmental outcomes for children prenatally exposed to buprenorphine is scarce. Given the growing use of buprenorphine as a maintenance treatment, research examining the long term effects of prenatal exposure to buprenorphine is crucial (Davids & Gastpar, 2004; Lintzeris, et al., 2006; Mattick, et al., 2003).

This study is the first of its kind to provide comprehensive, longitudinal data regarding the physical growth, neurological development, and temperament of children prenatally exposed to

methadone or buprenorphine in Australia. Additionally, this is the first study to describe these outcomes for infants prenatally exposed to buprenorphine, beyond the neonatal period. This research may be useful in supporting the approval of buprenorphine as a pharmaceutical maintenance treatment, in addition to the use of methadone, in pregnancy in clinical settings.

Of the 11 proposed hypotheses (see page 69-70), eight were supported. The results of this study showed that infants prenatally exposed to buprenorphine did not differ from non-exposed infants in their physical growth, neurological development, or temperament during the first two years of life. These findings add to the literature supporting the safety and efficacy of buprenorphine during pregnancy, the neonatal period, and early childhood. In addition, results showed that infants prenatally exposed to methadone fare more poorly than infants exposed to buprenorphine in terms of physical growth and early neurological development. It appears that methadone exposure *in utero* may continue to influence infant weight, until at least two years of age. Reassuringly, head circumference (HC) did not differ between the three groups of infants at any of the three follow-up assessments. HC is a key indicator of brain growth and cognitive development (García-Alix, et al., 2004; Noyola, et al., 2001), and the finding that the head growth of infants prenatally exposed to either methadone or buprenorphine was similar to that of non-exposed infants is important in providing support for the continuing use of both maintenance treatments during pregnancy.

In addition to having a pervasive influence on infant weight in early childhood, prenatal exposure to methadone may result in significant delays to visual maturation in early 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. However, neurodevelopmental outcome at 12 and 24 months of age, and

caregiver-rated infant temperament at 4-, 12- and 24-months, did not differ between infants prenatally exposed to methadone, buprenorphine, or non-exposed controls.

Results of the present study indicate that the quality of a child's care-giving environment has a strong influence over their cognitive, motor and behavioural development. This finding is consistent with previous research which has found socio-environmental factors to be important predictors of children's development (Lifschitz, et al., 1985; Messinger, et al., 2004; Tong, et al., 2006; Wilson, 1989). Additionally, results of the current study showed that mother-infant attachment at four months post-partum was the most important predictor of care-giver ratings of infant temperament at each of the three follow-up assessments. These results are consistent with previous research which has shown that maternal mental health influences mother-infant bonding and infant temperament (Austin, Hadzi-Pavlovic, Leader, Saint, & Parker, 2005; Edhborg, et al., 2000; Hans, et al., 1999; Najman, et al., 2000; Whiffen & Gotlib, 1989).

8.1 Study strengths and limitations

Strengths of the study

This is the first study to provide comprehensive data describing the longitudinal physical growth, neurological development, and temperament of infants and young children prenatally exposed to buprenorphine. This research contributes important knowledge regarding the safety and efficacy of buprenorphine as a maintenance treatment for pregnant women with opioid dependence. This is important because the number of women using illicit substances during pregnancy is high (Abdel-Latif, et al., 2007; Kennare, et al., 2005; Substance Abuse and Mental Health Services Administration, 2010). Whilst maintenance with methadone has traditionally been the first line treatment for pregnant women with opioid-dependence (Dunlop, et al., 2003; Farid, et al., 2008; Lintzeris, et al., 2006), there is evidence that increasing numbers of women are using buprenorphine as a maintenance treatment during pregnancy (Ebner, et al., 2007; Fischer, et al.,

2006; Gordon, 2006; R. E. Johnson, Jones, et al., 2003; Jones, et al., 2010; Lejeune, et al., 2006).

The high incidence of NAS and poorer early developmental outcomes for methadone-exposed infants, along with the stigma associated with methadone use, highlights the need for additional maintenance pharmacotherapies for pregnant opioid-dependent women (Davis & Templer, 1988; Hamilton, et al., 2010; Hans, 1989; Hunt, et al., 2008; Lifschitz, et al., 1983, 1985; Soepatmi, 1994).

There are several strengths of the present research. This is the first study to compare methadone with another active opioid treatment medication on the long-term outcomes examined. It is also the first study to compare the development of methadone-exposed infants with that of non-opioid exposed comparison infants in a prospective, rigorous and well-controlled study which considers many of the potential confounding factors that may influence infant development.

A second strength of the study was that the response (87%) and the retention (69%) rates were very good, particularly considering the characteristics of the study population. Previous longitudinal research with opioid-dependent women and their infants has been often been hampered by small sample sizes and poor rates of follow-up. For example, Wilson, Desmond and Verniaud (1973) examined the development, between the ages of three and 34 months, of 30 infants prenatally exposed to heroin. The authors reported that only 14 of these infants were followed-up for 12 months or longer, and commented that lack of parental cooperation in attendance at follow-up appointments posed a challenge to researchers. In another early study, Ramer and Lodge (1975) followed the development of 34 infants prenatally exposed to methadone maintenance, from birth to two years of age, however, numbers at each of the six follow-up assessments ranged from $n=4$ to $n=20$. Lifschitz and colleagues (1983, 1985; Wilson, et al., 1981) recruited 125 women and their infants in a longitudinal study examining infant development after prenatal opioid-exposure. Whilst 95% of participants were retained at the 12 month follow-up assessment, 57% were assessed at 3 years of age; whilst at the final follow-up

assessment when children were a mean age of 3.4 years, 74% of the original sample were retained. Soepatmi (1994) reported on the longitudinal development of 168 children exposed to illicit drugs (mainly heroin and methadone) in pregnancy. Of the 157 children who survived beyond the first year of life, only 67 (43%) were followed-up longer than 12 months. One hundred and forty four families were approached to participate in a follow-up study between three and 12 years later, of which 63% consented (Soepatmi, 1994). More recently, Hunt et al. (2008) examined the growth and cognitive development of 133 opiate-exposed infants and 103 non-exposed infants. Fifty nine percent of the total sample (140/236) participated in the follow-up assessment at 18 months of age, whilst at three years, 111 (47%) were assessed.

Women who use illicit substances are at increased risk of experiencing negative life events, such as mental health problems, domestic violence, transience, and financial hardship (Hans, et al., 1999; Nair, et al., 2003). All of these factors may make it difficult to engage them in longitudinal studies. The good response and retention rates in the present study were achieved by building strong relationships with participants, and with the staff from Drug and Alcohol Services South Australia (DASSA), the Women's and Children's Hospital (WCH), and Flinders Medical Centre (FMC). Substantial effort was required to engage and maintain contact with participating women and their infants. In order to maximise participation, I arranged to meet with many potential participants during the antenatal period, and apart from the two families who moved interstate, I individually conducted every follow-up assessment for each child in the study. Having a flexible schedule, which included contacting participants by telephone (usually mobile) or text message to remind them of study visits, and conducting home visits on weekends or after hours when this was more convenient for the families was also helpful. Whilst I visited families in their homes on average only yearly, I feel that this continuity and willingness to meet with the mothers and the children in their own environment was an important element in maintaining such high participation. Many of the women lived long distances from the hospital (in some cases up to five

hours drive away from Adelaide), and many did not drive, or were unable to afford the petrol to travel into the city. Additionally, the provision of a small financial compensation to participants, along with the gift of an educational toy or book for the children at each study visit, were appreciated and assisted in maintaining participation. Many families commented that the children greatly enjoyed the gifts, and at some visits I noticed that the books provided were the only ones a child owned.

Third, recruitment included all eligible women in the greater Adelaide area who wished to be maintained on buprenorphine throughout their pregnancy. Pregnant substance-dependent women in South Australia are usually referred to the high-risk pregnancy clinics at the Women's and Children's and Flinders Hospitals for antenatal care, thus we were able to recruit a reasonably high proportion of all eligible pregnant opioid-dependent women (see Chapter 3). We can be confident that results of the study may be generalisable to opioid-dependent women receiving maintenance treatment in South Australia, and their infants. The exception to this is that the current sample may not have been representative of indigenous opioid-dependent women receiving maintenance treatment in South Australia. The 2009 National Pharmacotherapy Statistics indicated that seven percent of pharmacotherapy clients in South Australia identified as being of Aboriginal and/or Torres Strait Islander (ATSI) origin (Australian Institute of Health and Welfare, 2010). However, in the current study, only two participating women (2.3%) reported their cultural background as ATSI. It is possible that some pregnant opioid-dependent indigenous women may have been residing in rural areas within South Australia and thus may have attended at regional health centres or hospitals for antenatal care.

Fourth, the inclusion of a non opioid-exposed control group of infants strengthened the design of this study and allowed for a comparison of development in a similar population of infants. Fourth, the use of VEP as a measure of infant neurological development at four months of age provided a

useful precursor to the later testing on the Bayley Scales of Infant Development, and may have helped address any examiner bias present in later neurological testing. Additionally, the use of valid and reliable measures, along with examiner training in the administration of the Bayley Scales of Infant Development, further consolidated the study design.

Finally, the longitudinal design of this research afforded some insight into relationships between prenatal exposure to opioids and later developmental outcomes. Longitudinal studies allow for inferences of cause and effect, and may assist in determining the predictive validity and stability of measures. Further, recall bias was limited due to the prospective, rather than retrospective, nature of data collection. Therefore, the longitudinal design of the research presented in this thesis was able to identify characteristics within families that were associated with better developmental outcomes for infants and young children.

Limitations of the study

The primary limitation of this study was that its parallel cohort design meant that participants were not randomly allocated to a treatment group. The incidence of opioid-dependent pregnancies in the Adelaide metropolitan area was not sufficient to support an adequately powered randomised controlled trial without an extended period of recruitment. Additionally, at the commencement of the longitudinal research study, research on the effects of prenatal exposure to buprenorphine was only just beginning to emerge and it was considered unethical to randomly assign women to a maintenance treatment. Consequently there may be unmeasured differences between the two maintenance groups that have independently influenced infant development. In order to try and address this issue, potential confounding variables were measured in detail and statistically controlled for in analyses. However, a consequence of this was possible loss of statistical power.

A second important limitation was the small sample size. While the study was designed to include all eligible opioid-dependent women in Adelaide, and recruitment was extended over five years, the numbers in each group were small and almost 20% of participants were lost to attrition over the course of the study. This means that analyses may have been underpowered and thus the possibility of making a Type II error was increased. Additionally, in order to ensure that the effect of prenatal exposure to buprenorphine was no worse than the current gold standard treatment (methadone) in terms of the infant outcomes for which there was no significant difference, a non-inferiority trial would have been appropriate. However, given the very large sample sizes required to conduct such trials, and the difficulty in recruiting the number of required participants, this sort of trial was not feasible for the current study.

A third limitation was that we did not have detailed information regarding women's substance use prior to study enrolment, nor was it possible to distinguish between use of licit and illicit forms of opioids or benzodiazepines at enrolment or during pregnancy. Self-reported substance use did not differ significantly between the BM and MM groups, and results of random urine drug screens conducted throughout pregnancy substantiated this data. A fourth limitation was that information about maternal mental health, socio-demographic factors and infant temperament was collected from only one informant. The use of multiple informants or mixed-methods, such as formal psychiatric assessment or inclusion of an observational component within the research protocol, would have strengthened the results, but was outside the scope of this study. Despite the strength of including a demographically similar non-opioid exposed comparison group, there may also be unmeasured differences (for example maternal medical or psychiatric co-morbidities) between the non opioid-using and the opioid-dependent groups.

Another limitation of this study was the inability to blind the examiner to each infant's group status. Initially this was attempted but became impossible to maintain, particularly as women in the control group often made their control status clear to the examiner at the first meeting. Thus, knowledge of the infants' exposure status presents an additional study confounder.

8.2 Implications and recommendations

Results from this study support the use of buprenorphine as an additional pharmacological maintenance treatment for opioid- dependent pregnant women, and thus have important direct clinical implications. Although research to date has supported the short-term safety and efficacy of buprenorphine during pregnancy and the early neonatal period (Fischer, et al., 2006; Jones, et al., 2005; Kakko, et al., 2008), studies of the longer term development of children exposed to buprenorphine are few (Kahila, Kivitie-Kallio, et al., 2007; Kayemba-Kay's & Laclyde, 2003; Salo, et al., 2009; Sandtorv, et al., 2009; Sarfi, et al., 2009; Schindler, et al., 2003). All have had limitations, such as low participant numbers, lack of comparison with existing treatments or non-exposed populations, failing to account for prenatal exposure to other substances, or providing inadequate information concerning methodology and outcomes. Previous research indicates that buprenorphine may provide some advantages over methadone in terms of neonatal outcomes, including increased birth weight, reductions in the incidence and severity of NAS and shorter hospital stays for exposed infants (Fischer, et al., 2006; Jones, et al., 2005; Jones, et al., 2010). The information presented in this thesis is consistent with previous research and strengthens the argument for buprenorphine to be approved for use in pregnancy.

Results showed that buprenorphine appears to confer advantages over methadone in terms of faster responses to VEP at four months of age, and healthy weight gain during early childhood. Whilst the advantages of buprenorphine did not extend to superior outcomes for infant cognitive, physical or behavioural development, or infant temperament, the findings of the present study

suggest that maternal use of buprenorphine in pregnancy appears to be as safe as methadone in terms of infant developmental outcomes. The benefits of buprenorphine, in terms of early infant neurodevelopment and healthy weight gain, suggest that it should be considered as a first line treatment for opioid dependence in pregnant women. Additionally, because there were few long term negative effects of methadone exposure, it would be reasonable to continue to offer it as a treatment option for opioid dependence during pregnancy if informed women wish to continue or commence maintenance with this treatment.

Results from this study also highlight the importance of a child's care-giving environment, and of early maternal mental health, in shaping future developmental outcomes. These findings suggest that there is a need to prioritise comprehensive mental health assessments for all opioid-dependent pregnant women, with a view to identifying social and psychological needs. Anecdotally, some women in the current study indicated that they felt socially isolated, with women in the two maintenance groups reporting in questionnaires that they were less satisfied with their level of social interaction and support than were women in the control group. Levels of psychological distress and postnatal depression, measured when infants were four months of age, were relatively high in the current study for all three groups of mothers. Almost one third of participating women reported experiencing significant psychological distress, and over one quarter reached criteria for probable minor postnatal depression (see Chapter 3). Given these high rates of problems, consideration should be given to prioritising and tailoring comprehensive, consistent, and supportive care to all opioid-dependent women during pregnancy which continues into the postnatal period and beyond if necessary. Further, results from this study show that prenatal exposure to marijuana and benzodiazepines has ongoing detrimental effects on children's neurological development. There was a high rate of other substance use reported by women during pregnancy in this study (see Table 3.4), with over one third of women reporting daily cannabis use (including 14% of the control group) and over 50% of maintained women and

12% of controls reporting benzodiazepine use during pregnancy. Taken together, these results suggest that early substance-use screening is an important aspect of antenatal care. Pregnant women should be asked specifically about their use of these substances and provided with information and advice about management as these substances can have unrecognised health effects on foetal development (Fried, 1989; Tansley, et al., 1986; Viggedal, et al., 1993).

Pregnancy may be an ideal time in which to engage substance-using women with appropriate services. Pregnancy and the impending birth may be seen as a strong motivator for some women in addressing their substance use issues. However, this may also be a time when social isolation increases as a woman distances herself from drug-using peers. Additionally, strained relationships with family, financial concerns, a history of abuse and trauma, or a partner's substances use may all influence maternal mental health and parenting capacity (New South Wales Department of Health, 2006a). Holistic services are required which address the developmental and safety needs of children, along with the psychosocial, health, and parenting needs of substance-using women and their partners. Ongoing programs, including outreach or home visiting services, may be needed to prevent relapse into substance use, and provide extra support when traditional pregnancy and postnatal services cease. Early interventions, including cognitive behavioural, mindfulness and attachment-based therapies, designed to strengthen maternal mental health, support maternal-infant attachment, and increase the quality of a child's care-giving environment, may enhance neurological development, behaviour, and temperament outcomes for at-risk infants (Dawe & Harnett, 2007; Dawe, Harnett, Rendalls, & Staiger, 2003; Nair, et al., 2003).

The present study provides new information regarding the developmental outcome of infants and young children prenatally exposed to buprenorphine or methadone. Results suggest that the physical growth, neurological development, and temperament of infants prenatally exposed to buprenorphine do not differ from that of non-exposed infants, over the first two years of life.

Additionally, maternal maintenance with buprenorphine appears to confer an advantage over methadone in terms of infant neural development at four months of age, and infant weight until at least two years of age. However, further research is needed to substantiate these findings. Future studies need to incorporate prospective longitudinal designs that follow exposed children into young adulthood if possible. Repeat testing of responses to VEP at later ages may assist in determining whether the difference in visual maturation, observed between the maintenance-exposed groups at four months of age, remains in later childhood. Studies involving larger sample sizes and randomisation of participants to treatment groups are important in providing high quality evidence. The use of multiple informants (including fathers) to provide information about parental mental health, socio-demographic factors, infant temperament and a child's care-giving environment would be an important addition to further research within this population. Nevertheless, the research presented in this thesis adds to the growing body of literature supporting the use of buprenorphine in pregnancy.

Finally, despite the high level of disadvantage and multiple risk factors experienced by families who participated in this research, it was heartening to see the majority of women and their infants doing well. The majority of children were in the care of their natural mother at two years of age and only one had been taken into state care. Additionally, most families had stable accommodation. Overall, it appeared that many of the infants in the study were extremely resilient, with no major health, development or behavioural problems. It is a possibility that the women who remained in the study were highly motivated and interested in their child's development. However, as a group they faced a number of hardships, and despite this they were able to provide a positive and nurturing environment for their children.

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

Volume Two

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Assessed for eligibility during pregnancy (*n*=147)

Enrolled after delivery
- (*n*=1 BM)

Excluded (*n*=19)
- Did not meet inclusion criteria (*n*=10)
- Unwilling to participate (*n*=9)

Enrolled (*n*=129/148, 87%)

Buprenorphine (*n*=52)
- Miscarriage (*n*=3)
- Termination (*n*=2)
- Withdrew (*n*=2)
- Infant diagnosed with autosomal defect (*n*=1)
- Moved interstate (*n*=1)
- 2nd child not eligible (*n*=4)

Eligible for early childhood phase (*n*=39/52, 75%)

Methadone (*n*=39)
- Lost to follow up (*n*=2)
- Termination (*n*=1)
- Drug interaction (*n*=1)
- Withdrew (*n*=2)
- Became ineligible (*n*=1)

Eligible for early childhood phase (*n*=32/39, 82%)

Control (*n*=38)
- Medical condition requiring treatment that could affect pregnancy (*n*=1)
- Miscarriage (*n*=1)
- Changed antenatal care (*n*=1)

Eligible for early childhood (*n*=35/38, 92%)

4-month asst

- Lost to follow-up (*n*=7)
- Withdrew (*n*=2)

Followed up at 4-months (*n*=30/39, 77%)

- Lost to follow up (*n*=4)
- Withdrew (*n*=3)
- Child died (*n*=1)

Followed up at 4-months (*n*=24/32, 75%)*
VEP data not collected for n=2

- Lost to follow up (*n*=1)
- Withdrew (*n*=1)

Followed up at 4-months (*n*=33/35, 94%)

12-month asst

- Lost to follow-up (*n*=2)

Followed up at 12-months (*n*=28/39, 72%)*
BSID-II data not collected for n=1

- Lost to follow up (n=1)
- Withdrew (n=1)

Followed up at 12-months (*n*=22/32, 69%)*
BSID-II data not collected for n=1

Followed up at 12-months (*n*=33/35, 94%)

24-month asst

- Lost to follow-up (n=4)

Followed up at 24-months (*n*=24/39, 62%)*
* Questionnaire not returned (n=1)*

- Lost to follow-up (*n*=3)

Followed up at 24-months (*n*=19/32, 59%)*
* Questionnaire not returned (n=1)*

- Lost to follow up (*n*=3)

Followed up at 24-months (*n*=30/35, 86%)

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

(highlight indicates the sample described in this thesis)

1

Table 2.1 Number of participants and retention rates for each assessment in the early childhood phase of the study

	Number of participants at each assessment		
Group Exposure Status	4 month	12 month	24 month
Buprenorphine-exposed	30	28 (93)	24 (86)
Methadone-exposed	24	22 (92)	19 (86)
Non-exposed control	33	33 (100)	30 (91)
Total	87	83 (95)	73 (88)

Note. One participant = one parent-infant dyad. Percentages shown in parentheses are retention from the previous assessment.

Table 2.2 Summary of data collected and measures used during each stage of the study

	Pregnancy & Neonatal Phase		Early Childhood Phase		
	Enrolment	Delivery/Neonatal period	4 months	12 months	24 months
Infant Measures					
Neurological Development		NAS scores	VEP	BSID-II	BSID-II
Psychological Development			STSI	STST	STST
Physical Development		GA; 1 & 5 min Apgar Scores; Growth parameters; medication prescribed for NAS	Growth parameters; sleep patterns; general health; BF status	Growth parameters; sleep patterns; general health; BF status	Growth parameters; sleep patterns; general health; BF status
Maternal Measures					
Obstetric History	Structured interview				
Parent/Child Interaction			MPAS	PSI	PSI
Parental Psychopathology			EPDS; GHQ	GHQ	GHQ
Social Support			ISSI	ISSI	ISSI
Environmental Measures					
Home Environment				HOME Inventory	HOME Inventory
Maternal Drug Use	Structured interview				
Demographic Information	Structured interview		Demographic questionnaire	Demographic questionnaire	Demographic questionnaire

Note. NAS=Neonatal Abstinence Syndrome; GA= Gestational Age; BF= Breast Feeding; VEP= Visual Evoked Potential; BSID-II= Bayley Scales of Infant Development-2nd Edition; STSI= Short Temperament Scale for Infants; STST= Short Temperament Scale for Toddlers; EPDS= Edinburgh Postnatal Depression Scale; MPAS = Maternal Postnatal Attachment Scale; ISSI= Interview Schedule for Social Interaction; HOME= Home Observation for Measurement of the Environment.

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

Note that actual testing was undertaken in a darkened room.
Photograph used with permission.

Table 2.3 Sample size estimates for primary outcome variables

Outcome Variable	BM group n	MM group n	BM group mean	MM group mean	Observed difference in means	Common SD (σ)	Observed effect size (δ)	Required n to detect the observed difference with 80% power
Neurological Development								
VEP 48' at 4 months	30	20	125.0	136.3	11.5	17.1	.67	36
VEP 69' at 4 months	30	22	121.0	135.0	14.0	23.8	.59	47
BSID-II MDI at 12 months	26	20	97.9	102.7	-4.8	8.9	.54	55
BSID-II PDI at 12 months	26	20	92.9	88.6	4.3	8.4	.51	61
BSID-II BRS at 12 months	25	20	123.5	120.0	3.5	8.3	.42	90
BSID-II MDI at 24 months	24	19	89.5	95.0	-5.5	14.5	.38	111
BSID-II PDI at 24 months	24	19	92.4	92.0	0.4	14.6	.03	>500
BSID-II BRS at 24 months	20	17	107.5	106.2	1.3	11.4	.11	>500
Psychological Development								
STSI EDS at 4 months	29	24	2.15	2.19	-0.04	0.5	.08	>500
STST EDS at 12 months	28	22	3.41	3.42	-0.01	0.5	.02	>500
STST EDS at 24 months	23	18	3.47	3.40	0.07	0.5	.14	>500

Table 2.3 continues

Table 2.3 continued

Outcome Variable	BM group *n*	MM group *n*	BM group mean	MM group mean	Observed difference in means	Common SD (σ)	Observed effect size (δ)	Required *n* to detect the observed difference with 80% power
Physical Development								
Weight at 4 months	30	22	6.5	5.9	0.6	0.7	.86	23
Length at 4 months	30	22	62.1	60.0	2.1	2.3	.91	20
HC at 4 months	30	22	41.0	40.3	0.7	1.2	.61	44
Weight at 12 months	27	22	10.0	9.2	0.8	1.2	.65	35
Length at 12 months	25	22	76.3	74.6	1.7	2.9	.59	47
HC at 12 months	27	22	46.5	46.2	0.3	1.2	.26	236
Weight at 24 months	24	19	13.0	12.0	1.0	1.4	.71	33
Length at 24 months	24	19	86.8	85.0	1.8	3.4	.53	57
HC at 24 months	23	17	48.5	48.1	0.4	0.9	.47	72

Note. VEP= Visual Evoked Potential; BSID-II= Bayley Scales of Infant Development-2nd Edition, STSI=Short Temperament Scale for Infants, STST=Short Temperament Scale for Toddlers

Table 3.1 Maternal characteristics at enrolment

	Control (*n*=33)	Buprenorphine (*n*=30)	Methadone (*n*=24)	*p*
Mother's age, M±SD (years)	26.30±6.18	28.03±5.50	28.29±6.13	.37
Gravida (% first)	33	17	21	.31
Parity (% first)	55	47	46	.76
Smoked in month prior to enrolment (% yes)	82	93	96	.24
Drank alcohol in month prior to enrolment (% yes)	42	50	32	.48
Gestation, M±SD (weeks), median (range)	23 (10-28)	15 (6-31)	18 (4-35)	.01
Mother's ethnicity (% Caucasian)	97	93	92	.73

Table 3.2 Differences in maternal characteristics at enrolment between study participants and non participants

	Participants (*n*=87)	Non participants (*n*=19[a])	*p*
Mother's age, M±SD (years)	27.45±5.94	25.56±6.53	.23
Gravida (% first)	23	17	.76
Parity (% first)	49	33	.30
Smoked in month prior to enrolment (%)	90	94	1.00
Drank alcohol in month prior to enrolment (%)	45	28	.20
Gestation, M±SD (weeks)	19.01±6.91	20.88±5.49[b]	.31
Mother's ethnicity (% Caucasian)	94	72[c]	.01

Note. [a]Data for the four BM women whose second infant was enrolled in the study are included in the participants column.

[b] Four non-participants were unaware of their gestational age at enrolment.

[c] Data missing from one woman.

Table 3.3 Maternal heroin use and maintenance therapy history

	Control (n=33)	Buprenorphine (n=30)	Methadone (n=24)	p
Age of first heroin use (years)[a]	$26.00\pm4.24_a$	$19.38\pm3.73_b$	$17.83\pm2.48_b$	<.01
Age first used heroin daily (years)	-	20.46 ± 3.53	18.83 ± 3.10	.09
Length of consistent heroin use prior to beginning maintenance therapy (months)	-	19.37 ± 23.22	24.37 ± 29.39	.45
Average daily heroin use prior to beginning maintenance therapy (no. times per day)	-	2.09 ± 1.23	2.76 ± 1.88	.13
Length of maintenance therapy (months), median (range)	-	7.5 (0-36)	10.0 (0-120)	.33

Note. Where no value is reported for the control group the reported *p*-value is the difference between the BM and MM groups. Values in the same row with different subscripts differ significantly at *p*<0.05 using bonferroni post hoc analyses. Values reported as *M±SD* unless otherwise indicated. *M±SD* reported in terms of the original distributions; however where data has been transformed *p*-values reported are for the transformed distributions.

[a]Two women in the control group reported using heroin 10 years prior to enrolment in the study; data was missing for one woman in the BM group.

Table 3.4 Self reported maternal substance use (%) during pregnancy

	Control (n=33)	Buprenorphine (n=30)	Methadone (n=24)	p
Tobacco	82	93	96	.24
Alcohol	64	62	59	.96
Heroin	-	50	42	.59
Other opioids[a]	21	32	41	.28
Cannabis	25_a	77_b	71_b	<.001
Benzodiazepines	12_a	40_b	50_b	<.01
Amphetamines	-	38	32	.77
Hallucinogens	0	7	0	.19
Antidepressant prescription medication	12	27	8	.21
Positive urine screen during pregnancy [b]	33_b	70_a	75_a	<.01

Note. Values reported as percentages. Values in the same row with different subscripts differ significantly at $p < .05$ using Fisher's exact tests. Where no value is reported for the control group the reported p-value is the difference between the BM and MM groups.

[a] Seven controls reported use of opioids, and four reported use of benzodiazepines during pregnancy.

[b] Urine drug screen results combined for opioids, benzodiazepines & cannabinoids. Three controls screened positive for other opioids, 8 for cannabis, and 2 for benzodiazepines.

Table 3.5 Neonatal characteristics and NAS treatment

	Control (n=33)	Buprenorphine (n=30)	Methadone (n=24)	p
Gender (% Male)	52	47	50	.93
Gestational age at delivery (weeks)[a]	38.85±1.89	38.73±1.95	38.08±1.89	.25
Born at term (% ≥ 37 weeks gestation)	91	90	83	.70
Birth Weight (gm)[c]	3241.82±535.97$_a$	3055.52±511.65$_{ab}$	2745.83±469.72$_b$	<.01
Low Birth Weight (% < 2500gm) [c]	12$_a$	14$_{ab}$	33$_b$	.13
Birth Length	49.32±3.21$_a$	47.93±2.54$_{ab}$	46.31±2.77$_b$	<.001
Birth HC	33.95±1.68$_a$	33.70±1.81$_{ab}$	32.68±1.28$_b$	.01
Apgar 1 minute, median (range)	9 (4-9)	9 (5-10)	9 (5-9)	1.00
Apgar 5 minutes, median (range)	9 (8-10)	9 (6-10)	9 (8-10)	.58

Table continues

Table 3.5 continued.

	Control (n=33)	Buprenorphine (n=30)	Methadone (n=24)	p
Mean Finnegan Score[b,d]	$1.26\pm1.06_a$	$3.70\pm1.51_b$	$4.02\pm1.47_b$	<.001
Maximum Finnegan Score[d]	$3.71\pm2.37_a$	$10.87\pm3.20_b$	$12.00\pm3.56_b$	<.001
Range of Finnegan Scores	0-12	0-18	0-21	-
Received any pharmacological treatment for NAS (% yes)	-	47	50	.81
Received Morphine (% yes)	-	43	50	.78
Received Phenobarbital (% yes)	-	10	0	.25

Note. Values reported as M±SD unless otherwise indicated. *M±SD* reported in terms of the original distributions; however where data has been transformed reported *p*-values are for the transformed distributions. Values in the same row with different subscripts differ significantly at *p* < .05 using Bonferroni post hoc analyses. Where no value is reported for the control group the reported *p*-value is the difference between the BM and MM groups.

[a]Power 4 transformation used in analysis.

[b]Square root transformation used in analysis.

[c]Data missing for one BM infant.

[d]Data missing for two control infants.

Table 3.6 Demographic characteristics of participating infants and families (*N*=87)

	Control (*n*=33)	Buprenorphine (*n*=30)	Methadone (*n*=24)	*p*
Still breastfed (%)	48	43	38	.71
Parent reported medical problem (%)	45	50	42	.83
Poor sleeper (% meeting Sadeh's criteria[a])	21	23	17	.89
Number of children in household				
Only child	52	53	54	.95
One other child	27	27	29	
Two other children	9	13	8	
Three or more other children	12	7	8	
Family Structure (% sole parent)	12	30	38	.07
Mother's education (% <high school)	48	53	67	.38
	(*n*=29)	(*n*=22)	(*n*=14[c])	
Father's education (% <high school)[b]	55	45	79	.13
Father not in paid employment (%)[b]	21$_a$	32$_{ab}$	64$_b$	.02
	(*n*=31)	(*n*=28)	(*n*=20)	
Household Income p/a (%≤$31,200)[d]	48$_a$	64$_{ab}$	85$_b$	.03

Table continues

Table 3.6 continued

	Control	Buprenorphine	Methadone	p
	(n=33)	(n=30)	(n=24)	
Accommodation (% Government subsidised) [e]	15$_a$	26$_{ab}$	46$_b$	.04
Family moved house ≥1 time since child's birth	15	20	21	.23

Note. Values reported as percentages. Values in the same row with different subscripts differ significantly at $p < .05$ using Fisher's exact tests.

[a] Sadeh's criteria for poor sleep defined as one or more of the following: a) waking >3 times per night; b) nocturnal wakefulness of >1 hour; or c) total sleep time (including day and night sleeps) <9 hours {Sadeh, 2004 #247}.

[b] Father's education and employment status reported only for families where father lived in child's household.

[c] Parental figures for one MM family were 2 females.

[d] data missing for 2 control, 2 BM and 4 MM families.

[e] data missing for 3 BM families.

Table 3.7 Maternal Postnatal Attachment Scale scores, by group.

	Control	Buprenorphine	Methadone	p
	(n=33)	(n=30)	(n=24)[a]	
Subscale Scores, median (range)				
Quality of attachment	43.60 (35.10-45.00)	42.20 (37.69-45.00)	44.30 (38.20-45.00)	.10
Absence of Hostility	21.60 (12.60-25.00)	21.80 (16.20-25.00)	22.80 (14.90-25.00)	.16
Postnatal Pleasure in interaction	23.00 (16.00-25.00)	22.75 (16.00-25.00)	23.75 (20.00-25.00)	.27
Global Attachment Score ($M\pm SD$)[b]	85.84±6.74	86.56±5.17	88.64±4.28	.21
Lowest quartile of Global scores (%)	30	30	13	.30

Note. Higher scores indicate higher levels of attachment.

[a]The Postnatal Pleasure in Interaction and Global scores could not be calculated for one MM woman.

[b]$M\pm SD$ reported in terms of the original distribution, however the reported p-value was calculated using the transformed

(power 5) data.

Table 3.8 Edinburgh Postnatal Depression Scale and General Health Questionnaire scores, by group.

	Control	Buprenorphine	Methadone	*p*
	(*n*=33)	(*n*=30)	(*n*=24)	
Edinburgh Postnatal Depression Scale				
EPDS Total Score (*M±SD*)[a]	6.06±4.55	7.41±5.18	8.00±5.60	.42
EPDS Probable Minor Depression (% ≥10)	15$_a$	27$_{ab}$	42$_b$	.08
EPDS Probable Major Depression (% ≥13)	12	13	29	.23
General Health Questionnaire				
GHQ Total Score, median (range)	2.00 (0.00-17.00)	2.50 (0.00-20.00)	3.50 (0.00-21.00)	.43
Significant Psychological Distress (% ≥6)	30	33	33	1.00

Note. Values in the same row with different subscripts differ significantly at *p*=.05 using Fisher's exact tests. Higher scores on the EPDS & GHQ indicate greater severity of symptoms.

[a] *M±SD* reported in terms of the original distribution, however the reported *p*-value was calculated using the transformed (square root + 1) data.

Table 3.9 Interview Schedule for Social Interaction-Short Form (ISSI-SF) scores, by group

	Control	Buprenorphine	Methadone	p
	(n=33)	(n=30)	(n=24)	
ISSI-SF Subscales, median (range)				
Availability of Attachment	6.00 (0.00-6.00)$_a$	5.00 (0.00-6.00)$_{ab}$	5.00 (0.00-6.00)$_b$	.08
Adequacy of Attachment	8.00 (0.00-10.00)	6.00 (0.00-10.00)	5.78 (0.00-10.00)	.21
Availability of Social Interaction	2.00 (0.00-6.00)	2.00 (0.00-6.00)	1.00 (0.00-6.00)	.28
Adequacy of Social Interaction	7.00 (0.00-8.00)	5.86 (1.00-8.00)	6.00 (0.00-8.00)	.18
ISSI-SF Total Score ($M\pm SD$)	20.18±6.63$_a$	17.33±7.12$_{ab}$	15.29±8.82$_b$	.05

Note. Higher scores indicate better perceived social support. Values in the same row with different subscripts differ

significantly at $p \leq .05$ using Mann-Whitney U (for comparison of median scores) or Bonferroni post hoc (for comparison of

mean scores) analyses.

Table 3.10 Self-reported maternal substance use in the month prior to the four month follow-up assessment

	Control (*n*=33)	Buprenorphine (*n*=30)	Methadone (*n*=24)	*p*
Tobacco	76	90	96	.08
Alcohol	63$_a$	37$_b$	33$_b$	.04
Psychotropic prescription medication [a]	9	13	13	.84
Any illicit drug use	21$_a$	57$_b$	75$_b$	<.001
Heroin	-	17	29	.33
Other opioids	-	-	-	-
Cannabis	21	47	46	.06
Benzodiazepines	-	20	21	1.00
Amphetamines	-	17	17	1.00

Note. Values reported as percentages. Values in the same row with different subscripts differ significantly at *p* < .05 using Fisher's exact tests. Where no value is reported for the control group the reported *p*-value is the difference between the BM and MM groups.

[a] Psychotropic prescription medication includes antidepressant and anti-psychotic drugs.

Table 3.11 Parenting Stress Index and HOME Inventory Total Scores, by group

	Control	Buprenorphine	Methadone	p
12 months	(n=33)	(n=28)	(n=22)	
PSI Parent Domain Total Score[a]	118.37±26.35	132.16±20.77	118.17±29.13	.08
Total HOME score [b,c]	36.75±4.44	37.41±3.24	36.84±3.05	.80
24 months	(n=30	(n=24)	(n=19)	
PSI Parent Domain Total Score[d]	118.98±25.75	136.12±30.20	122.27±18.65	.10
Total HOME score[e]	37.98±3.48$_{ab}$	36.66±3.94$_a$	40.00±3.25$_b$	.02

Note. Values reported as *M±SD.* Values in the same row with different subscripts differ significantly at *p* ≤ .05 using Bonferroni post hoc analyses.

PSI= Parenting Stress Index (higher scores indicate greater dysfunction), HOME= Home Observation for Measurement of the Environment (higher scores indicate a more child-centred home environment).

[a] PSI Total score could not be calculated for 1 control, 2 BM and 3 MM families.

[b] Total HOME score could not be calculated for 2 MM families.

[c] *M±SD* reported in terms of the original distribution, however the reported *p*-value was calculated using the transformed (squared) data.

[d] PSI Total score could not be calculated for 4 control, 7 BM and 5 MM families.

[e] Total HOME score could not be calculated for 2 control, 1 BM and 3 MM families.

Table 4.1 Anthropometry of infants at 4, 12 and 24 months of age

	Control	Buprenorphine	Methadone	p
4 months	(n=33)	(n=30)	(n=22)[a]	
Weight (kg)[b]	6.67±1.00$_a$	6.53±0.84$_a$	5.91±0.55$_b$	<.01
Length (cm)	62.7 (57.4-68.7)$_a$	61.5 (57.5-68.5)$_{ab}$	60.3 (56.3-63.3)$_b$	.01
HC (cm)	41.4 (38.5-44.5)$_a$	41.1 (38.0-44.1)$_{ab}$	40.4 (39.2-42.2)$_b$	.02
12 months	(n=33)	(n=27)[c]	(n=22)	
Weight (kg)	10.17±1.34$_a$	9.95±1.13$_{ab}$	9.22±1.21$_b$	.02
Length (cm)[d]	76.8±3.3$_a$	76.3±3.0$_{ab}$	74.6±2.8$_b$	.03
HC (cm)	46.8±1.7	46.5±1.2	46.2±1.1	.29
24 months	(n=30)	(n=24)	(n=19)	
Weight (kg)	13.31±1.79$_a$	13.00±1.51$_{ab}$	12.01±1.23$_b$	.02
Length (cm) [e,f]	87.2±4.1	86.8±3.8	85.0±3.0	.15
HC (cm) [g]	49.3 (45.0-52.0)$_a$	48.6 (46.5-50.5)$_{ab}$	48.1 (46.9-49.3)$_b$	.02

Note. Values reported as $M±SD$ or median (range). $M±SD$ reported in terms of the original distributions; however where data has been transformed, reported p-values are for the transformed distributions. Values in the same row with different subscripts differ significantly at p ≤ .05 using Bonferroni post hoc (for comparison of mean scores) or Mann-Whitney U (for comparison of median scores) analyses.

[a] Data missing for two MM children.

[b] Inverse square transformation.

[c] Data missing for one BM child.

[d] Data missing for two BM children.

[e] Inverse cube transformation.

[f] data missing for two MM children.

[g] data missing for one control, one BM and 5 MM children

Table 4.2 Multiple Regression Analysis for variables predicting weight (in kg) at four months of age (*N*=84)

Variable	*B±SE B*	Standardised regression coefficients (β)
Birth Weight	0.73±0.21	-.42**
Gestational age at delivery	-0.01±0.06	-.02
Gender (male)	0.55±0.16	.34***
Group		
Control	0	
Buprenorphine	-0.04±0.18	-.01
Methadone	-0.38±0.20	.19

Note. For the regression model as a whole, R^2=.44, $F_{(5,78)}$=12.14, $p<.0001$. *B±SE B* reported in terms of the original distributions; however β, R^2 & *F* values reported in terms of the transformed (inverse square) data.

*$p<.05$, ** $p<.01$, ***$p<.001$, †$p<.0001$

Table 4.3 Multiple Regression Analysis for variables predicting length (in cm) at four months of age (*N*=85)

Variable	*B±SE B*	Standardised regression coefficients (β)
Birth Length	0.36±0.11	.39**
Gestational age at delivery	0.33±0.17	.23*
Gender (male)	1.72±0.45	.31***
Group		
Control	0	
Buprenorphine	0.40±0.53	.07
Methadone	-0.87±0.61	-.14

Note. For the regression model as a whole, R^2=.50, $F(5,79)$=16.08, p<.0001.*p<.05, ** p<.01, ***p<.001, †p<.0001

Table 4.4 Multiple Regression Analysis for variables predicting head circumference (in cm) at four months of age (*N*=85)

Variable	*B±SE B*	Standardised regression coefficients (β)
Birth HC	0.45±0.09	.54***
Gestational age at delivery	-0.04±0.07	-.05
Gender (male)	.081±0.25	.28**
Group		
Control	0	
Buprenorphine	-0.36±0.28	-.12
Methadone	-0.52±0.32	-.16

Note. For the regression model as a whole, R^2=.47, F(5,79)=13.90, *p*<.0001. **p*<.05, **

p<.01, ***p<.001, †*p*<.0001

Table 4.5 Multiple Regression Analysis for variables predicting weight (in kg) at 12 months of age (*N*=81)

Variable	$B \pm SE\ B$	Standardised regression coefficients (β)
Birth Weight	0.64±0.25	.28*
Gender (male)	0.74±0.25	.29**
Group		
Control	0	
Buprenorphine	-0.11±0.30	-.04
Methadone	-0.62±0.33	-.22

Note. For the regression model as a whole, R^2=.27, F(4,76)=7.08, *p*<.001. **p*<.05, ** *p*<.01, ***p<.001, †*p*<.0001

Table 4.6 Multiple Regression Analysis for variables predicting length (in cm) at 12 months of age (*N*=80)

Variable	*B±SE B*	Standardised regression coefficients (β)
Birth Length	0.37±0.15	.37*
Gestational age at delivery	0.25±.024	.06
Gender (male)	1.86±0.62	.28**
Group		
Control	0	
Buprenorphine	1.00±0.90	.00
Methadone	0.19±1.06	-.15

Note. For the regression model as a whole, R^2=.32, F(5,74)=7.01, *p*<.0001. **p*<.05, ** *p*<.01, ****p*<.001, †*p*<.0001

Table 4.7 Multiple Regression Analysis for variables predicting head circumference (in cm) at 12 months of age (*N*=79)

Variable	*B±SE B*	Standardised regression coefficients (β)
Birth HC	0.30±0.08	.36**
Alcohol use (yes)[a]	0.46±0.28	.16
Gender (male)	0.96±0.28	.33**
Group		
Control	0	
Buprenorphine	-0.18±0.31	-.06
Methadone	-0.17±0.35	-.06

Note. For the regression model as a whole, R^2=.36, F(5,73)=8.18, *p*<.0001.

B±SE B reported in terms of the original distributions; however β, R^2 & *F* values reported in terms of the transformed (square) data. *p*<.05, ** *p*<.01, ***p*<.001, †*p*<.0001

[a] Self-reported use during pregnancy.

Table 4.8 Multiple Regression Analysis for variables predicting weight (in kg) at 24 months of age (_N_=72)

Variable	$B \pm SE\ B$	Standardised regression coefficients (β)
Birth Weight	0.80±0.31	.27*
Gender (male)	1.25±0.33	.39***
Group		
Control	0	
Buprenorphine	-0.09±0.39	-.07
Methadone	-0.85±0.43	-.24*

Note. For the regression model as a whole, R^2=.35, $F(4,67)$=9.18, $p<.0001$.

_B±SE B_ reported in terms of the original distributions; however β, R^2 & _F_ values reported in terms of the transformed (power 5) data.*$p<.05$, ** $p<.01$, ***$p<.001$, †$p<.0001$

Table 4.9 Multiple Regression Analysis for variables predicting length (in cm) at 24 months of age (*N*=71)

Variable	*B±SE B*	Standardised regression coefficients (β)
Birth Length	0.43±0.13	.36**
Gender (male)	2.83±0.77	.37***
Group		
Control	0	
Buprenorphine	0.34±0.91	.04
Methadone	-0.93±1.06	-.10

Note. For the regression model as a whole, R^2=.33, $F_{(4,66)}$=7.97, $p<.0001$.

*$p<.05$, ** $p<.01$, ***$p<.001$, †$p<.0001$

Table 4.10 Multiple Regression Analysis for variables predicting head circumference (in cm) at 24 months of age (*N*=66)

Variable	*B±SE B*	Standardised regression coefficients (β)
Birth HC	0.22±0.08	.28**
Gender (male)	1.30±0.28	.47***
Group		
Control	0	
Buprenorphine	-0.02±0.41	-.16
Methadone	-0.15±0.49	-.20

Note. For the regression model as a whole, R^2=.43, $F(4,61)$=11.30, *p*<.0001.

p<.05, ** *p*<.01, ***p*<.001, †*p*<.0001
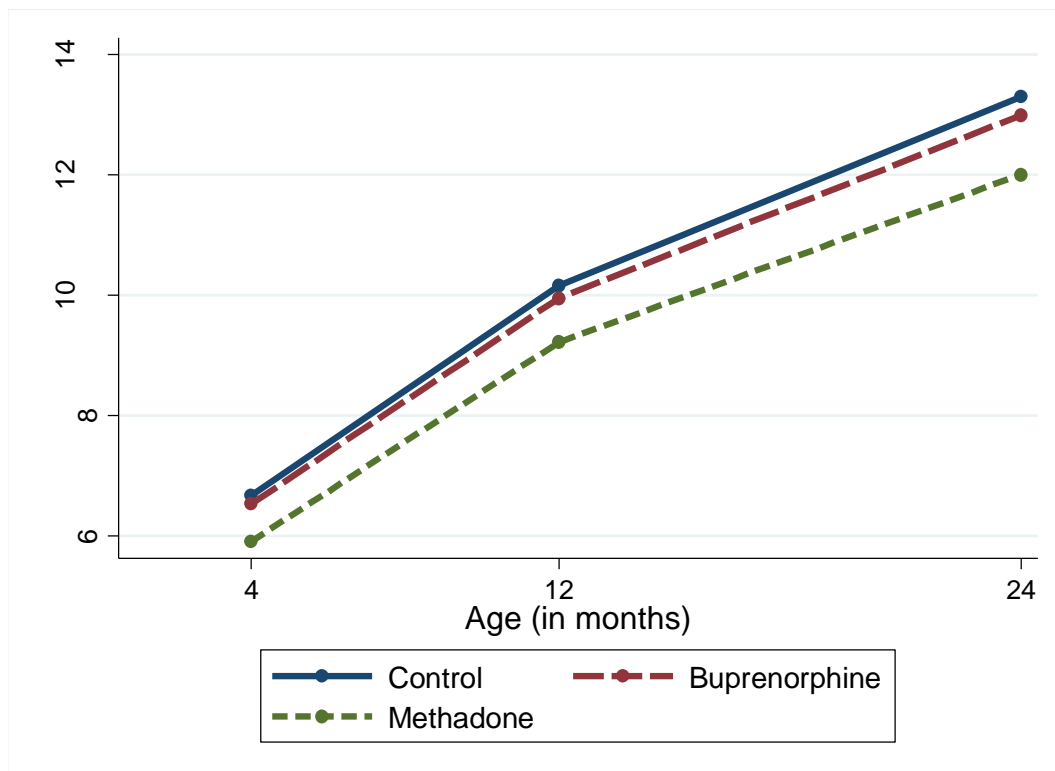
Figure 4.1 Mean weight for each group at the 4-, 12- and 24-month follow-up assessments.
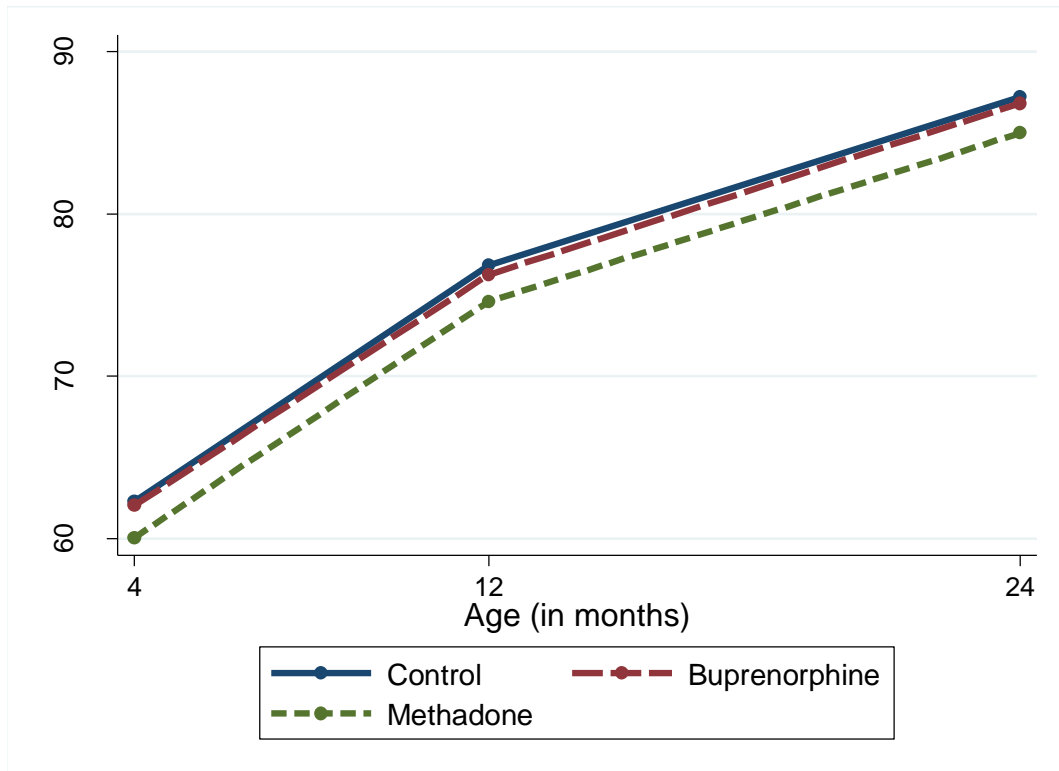
Figure 4.2 Mean length for each group at the 4-, 12- and 24-month follow-up assessments.
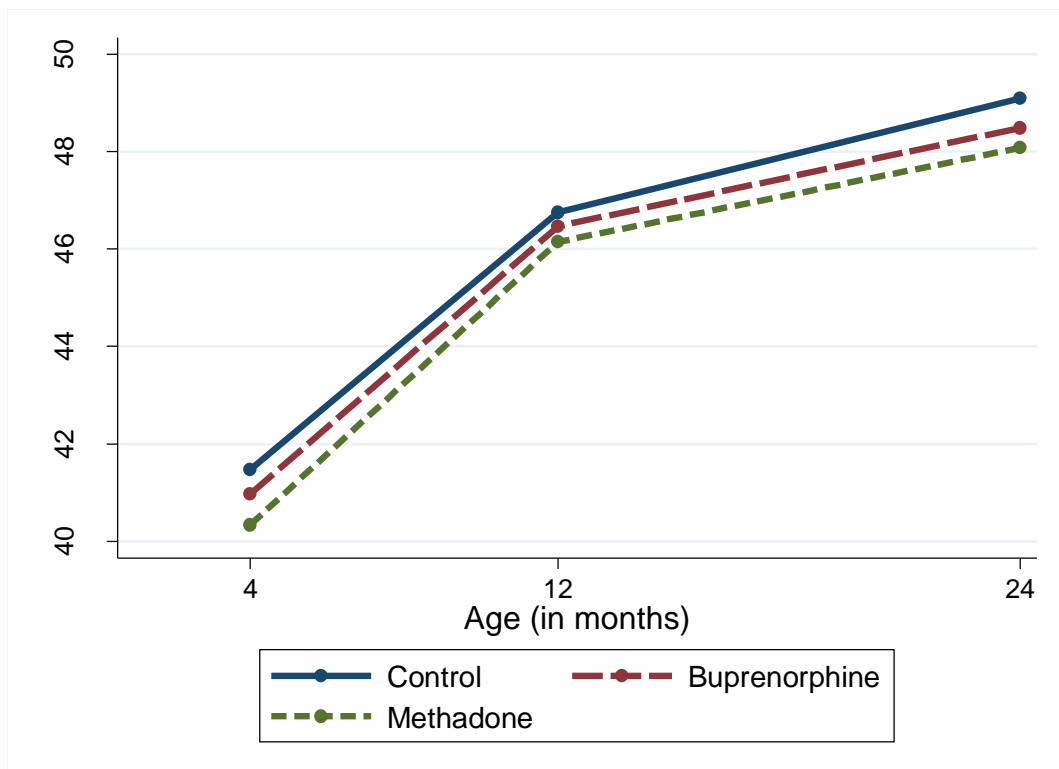
Figure 4.3 Mean head circumference for each group at the 4-, 12- and 24-month follow-up assessments.

Table 5.1 Characteristics of participating women and infants, for VEP analyses

	Control (n=33)	Buprenorphine (n=30)	Methadone (n=22)	p
Maternal variables at enrolment				
Mother's age, M±SD (years)	26.30±6.18	28.03±5.50	28.41±6.28	.36
Parity (% first)	55	47	45	.75
Gravida (% first)	33	20	18	.34
Gestational Age, M±SD (weeks)	21.45±4.41$_a$	16.83±7.99$_b$	18.23±7.86$_{ab}$	.03
Smoked in month prior (% yes)	82	93	95	.21
Alcohol in month prior (% yes)	42	50	29	.32
Infant characteristics				
Gender (% Male)	52	47	45	.89
Gestational age at delivery, M±SD (weeks)	38.85±1.89	38.73±1.95	38.09±1.95	.33
Birth Weight, M±SD (grams)	3241.82±535.97$_a$	3055.52±511.65$_{ab}$	2749.09±484.32$_b$	<.01

Table 5.1 continues

Table 5.1 continued

	Control	Buprenorphine	Methadone	P
	(*n*=33)	(*n*=30)	(*n*=22)	
Birth Length, M±SD (cm)	49.32±3.21$_a$	47.93±2.54$_{ab}$	46.52±2.52$_b$	<.01
Birth Head Circumference, M±SD (cm)	33.95±1.68$_a$	33.70±1.81$_{ab}$	32.65±1.34$_b$	.02
Age at testing, M±SD (weeks)	16.77±1.23	18.02±3.45	16.86±1.96	.09
Corrected age at testing , M±SD (weeks) [a]	15.62±2.33	16.76±4.20	14.95±2.02	.10
Received any pharmacological treatment for NAS (% yes)	-	47	50	.81
Family characteristics at follow-up				
Family Structure (% sole parent)	12	30	36	.09
Father Unemployed (% yes)	21$_a$	43$_{ab}$	63$_b$	.02
Household Income p/a (%≤$A31,200)	48$_a$	68$_{ab}$	83$_b$	.04
Accommodation (% Government subsidised)	15$_a$	32$_{ab}$	50$_b$	.02

Note. Values in the same row with different subscripts differ significantly at $p < .05$ using Chi^2 analyses.

Where no value is reported for the control group, the *p*-value is the difference between the BM and MM groups.

[a]Corrected age = age at testing + gestational age - 40 wks.

Table 5.2 VEP Latencies at four months of age, by group

VEP viewing field	Control	Buprenorphine	Methadone	p
48' retinal arc[a]	(n=33)	(n=30)	(n=20)	
	124.34±12.35	124.97±16.08	136.25±18.02	<.01
69' retinal arc[a]	(n=33)	(n=30)	(n=22)	
	119.92±11.74	121.02±14.10	134.99±33.46	.02

Note. *M±SD* reported in terms of the original distributions; *p*-values reported in terms of the transformed data (inverse square transformation).

[a] A minute (') of retinal arc is a unit of angular distance.

Table 5.3 Maternal substance use, by group, for VEP analyses

	Control (*n*=33)	Buprenorphine (*n*=30)	Methadone (*n*=22)	*p*
1. Mother's heroin use				
Age of first heroin use, M±SD (years)[a]	26.00±4.24	19.38±3.72	17.82±2.52	.10
Age first used heroin daily, M±SD (years)	-	20.46±3.53	18.90±3.18	.12
Length of consistent heroin use prior to beginning maintenance therapy, M±SD (months)	-	19.37±23.22	25.67±29.67	.43
Average daily use prior to beginning maintenance therapy, M±SD (no. times used)	-	2.09±1.23	2.86±1.92	.10
Length of current maintenance treatment, M±SD (months)	-	9.63±8.52	17.75±25.73	.11
2. Detailed drug use prior to conception	Not available	Not available	Not available	

Table 5.3 continues

Table 5.3 continued

	Control (n=33)	Buprenorphine (n=30)	Methadone (n=22)	p
3. At enrolment into the study (% Yes within previous month)				
Tobacco	82	93	95	.29
Alcohol	42	50	29	.34
Heroin	-	34	29	.76
Other opioids[b]	3	19	19	.09
Cannabis	22$_a$	66$_b$	55$_b$	<.01
Benzodiazepines	-	10	19	.43
Amphetamines	-	17	14	1.00
Psychotropic prescription medication (antidepressants)	6	21	5	.13

Table 5.3 continues

Table 5.3 continued

	Control (*n*=33)	Buprenorphine (*n*=30)	Methadone (*n*=22)	*p*
Opioid prescription medication	Not available	Not available	Not available	
4.During pregnancy (% Yes)				
Tobacco	82	90	95	.30
Alcohol	64	50	55	.55
Heroin	-	50	41	.58
Other opioids[b]	21	30	36	.45
Cannabis	24$_a$	77$_b$	73$_b$	<.001
Benzodiazepines	12$_a$	40$_b$	45$_b$	.01
Amphetamines	-	33	32	1.00
Psychotropic prescription medication (antidepressants)	12	27	9	.21

Table 5.3 continued

	Control (*n*=33)	Buprenorphine (*n*=30)	Methadone (*n*=22)	*p*
Opioid prescription medication	Not available	Not available	Not available	
5. Positive urine drug screen during pregnancy (% yes)[c]	33_a	70_b	77_b	<.01
6. At 4 months post delivery (% Yes)				
Tobacco	79_a	90_{ab}	100_b	.05
Alcohol	64_a	33_b	36_{ab}	.04
Heroin	-	30	35	.76
Other opioids	-	3	5	1.00
Cannabis	22_a	57_b	50_b	.01
Benzodiazepines	-	23	23	1.00
Amphetamines	-	17	23	.73
Psychotropic prescription medication (any)	6	17	9	.45
Opioid prescription medication	-	-	-	-

Table 5.3 Note. Values in the same row with different subscripts differ significantly at p < .05 using Fisher's exact tests.

Where no value is reported for the control group, the *p*-value is the difference between the BM and MM groups.

[a]Two women in the control group reported using heroin 10 years prior to enrolment in the study, Note continued.

[b]One control subject reported use of an opioid at enrolment, 7 controls reported use of opioids and 4 reported use of a benzodiazepine during pregnancy. Whether these substances were used licitly or illicitly was not reported.

[c]Urine drug screen results were for opioids, benzodiazepines & cannabinoids only. Three controls screened positive for opioids, 8 for cannabis, 2 for benzodiazepines.

Table 5.4 Multiple Regression Analysis for variables predicting VEP response to 48' checks

(*N*=76)

Variable	*B*±*SE B* (milliseconds)	Standardised regression coefficients (β)
Corrected Age	-2.14±0.53	0.36**
Family Income (<$31, 200)	-10.20±3.50	0.31**
VEP equipment (2nd)	9.86±4.42	-0.19
Marijuana use in pregnancy (yes)	4.88±3.78	-0.23*
Group		
Control	0	
Buprenorphine	1.04±4.19	0.04
Methadone	12.54±4.49	-0.30*

Note. For the regression model as a whole, R^2=.33, $F(6,69)$ = 5.64, $p<.001$.

B±*SE B* reported in terms of the original distributions; β, R^2 & *F* values reported in terms of the transformed data (inverse square transformation).

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

Table 5.5 Multiple Regression Analysis for variables predicting VEP response to 69' checks (*N*=77)

Variable	*B±SE B* (milliseconds)	Standardised regression coefficients (β)
Corrected Age	-2.04±0.49	0.46**
Family Income (<$31, 200)	-5.73±3.26	0.16
VEP equipment (2nd)	9.89±4.12	-0.18
Marijuana use in pregnancy (yes)	5.33±3.52	-0.25*
Group		
Control	0	
Buprenorphine	0.08±3.90	-0.04
Methadone	7.75±4.13	-0.16

Note. For the regression model as a whole, R^2=.34, F(6,70) = 5.98, *p*<.0001.

B±SE B reported in terms of the original distributions; β, R^2 & *F* values reported in terms of the transformed data (inverse square transformation). *p*<.05, ** *p*<.01.

Table 6.1 Index scores of the Bayley Scales of Infant Development at 12 and 24 months of age, by group

Bayley Scales of Infant Development	Control	Buprenorphine	Methadone	*p*
12 months [a]	(*n*=33)	(*n*=27)	(*n*=21)	
Mental Developmental Index, *M±SD*[b]	100.5±9.9	97.9±10.6	102.7±7.1	.25
Some delay (% MDI <1 *SD* below the mean)	6	11	0	.36
Psychomotor Developmental Index, *M±SD*	92.6±11.7	92.9±9.8	88.6±7.0	.28
Some delay (% PDI <1 *SD* below the mean)	21	11	19	.66
Behavior Rating Scale Total Score, *M±SD*[c]	120.1±7.7	123.5±7.3	120.0±9.2	.22
Below 'normal limits' (% BRS ≤25 percentile)	17	12	25	.51
24 months	(*n*=30)	(*n*=24)	(*n*=19)	
Mental Developmental Index (med, range)	97.5 (76-118)	87.0 (61-112)	98.0 (62-112)	.25
Some delay (% MDI <1 *SD* below the mean)	27	42	21	.32

Table 6.1 continues.

Table 6.1 continued.

	Control	Buprenorphine	Methadone	*p*
24 months	(*n*=30)	(*n*=24)	(*n*=19)	
Psychomotor Developmental Index, *M±SD*	95.7±13.95	92.4±14.2	92.0±15.0	.59
Some delay (% PDI <1 *SD* below the mean)	27	33	26	.83
Behavior Rating Scale Total Score, *M±SD*[d]	108.1±8.8	107.5±12.2	106.2±10.6	.84
Below 'normal limits' (% BRS ≤25 percentile)	28	25	29	.96

Notes: Values reported as *M±SD* or median (range), and percentages where indicated. *M±SD* reported in terms of the original

distributions; however where data has been transformed, reported *p*-values are for the transformed distributions.

[a] Data missing for one BM and one MM child.

[b] Square transformation.

[c] n for control=30, BM=25, MM=20

[d] n for control=29, BM=20, MM=17

Table 6.2 Multiple Regression Analysis for variables predicting MDI scores at 12 months of age (N=80)

Variable	$B \pm SE\ B$	Standardized regression coefficients (β)
ISSI-SF Total Score (4mths)	0.26±0.14	.22
Total HOME Score (12mths)	0.74±0.28	.27*
Group		
Control	0	
Buprenorphine	-2.42±2.35	-.12
Methadone	3.65±2.59	.16

Note. For the regression model as a whole, R^2=.18, $F(4,75) = 4.10$, $p<.01$.

$B \pm SE\ B$ reported in terms of the original distributions; β, R^2 & F values reported in terms of the transformed data (power 2.5 transformation). *$p<.05$, ** $p<.01$.

Table 6.3 Multiple Regression Analysis for variables predicting PDI scores at 12 months of age (N=81)

Variable	$B \pm SE\ B$	Standardized regression coefficients (β)
Birth HC	1.33±0.66	.24*
Group		
Control	0	
Buprenorphine	0.72±2.55	.03
Methadone	-2.36±2.84	-.12

Note. For the regression model as a whole, R^2=.09, $F(3,77) = 2.62$, $p=.06$.

$B \pm SE\ B$ reported in terms of the original distributions; however β, R^2 & F values reported in terms of the transformed data (square transformation). *$p<.05$.

Table 6.4 Multiple Regression Analysis for variables predicting BRS scores at

12 months of age (*N*=74)

Variable	$B \pm SE\ B$	Standardized regression coefficients (β)
Infant gender (male)	-4.91±1.78	-.31**
ISSI-SF Total Score (4mths)	-0.03±0.13	-.03
Total HOME Score (12mths)	0.56±0.25	.26*
Group		
Control	0	
Buprenorphine	2.46±2.10	.14
Methadone	-0.88±2.31	-.05

Note. For the regression model as a whole, R^2=.22, F(5,68) = 3.72, *p*<.01.

B±SE B reported in terms of the original distributions; however β, R^2 & *F* values reported in terms of the transformed data (square root transformation). *p*<.05, ** *p*<.01

Table 6.5 Multiple Regression Analysis for variables predicting MDI scores at 24 months of age (*N*=67)

Variable	$B \pm SE\ B$	Standardized regression coefficients (β)
Benzodiazepine use (yes)[a]	-8.50±3.87	-.27*
ISSI-SF Total Score (4mths)	0.05±0.24	.04
Total HOME Score (24mths)	1.65±0.48	.44**
Group		
Control	0	
Buprenorphine	-2.67±3.71	-.08
Methadone	-1.75±4.47	-.05

Note. For the regression model as a whole, R^2=.30, F(5,61) = 5.21, p<.001.

$B \pm SE\ B$ reported in terms of the original distributions; however β, R^2 & *F* values reported in terms of the transformed data (square transformation). *p<.05, ** p<.01, ***p<.001

[a] Maternal self-reported use during pregnancy.

Table 6.6 Multiple Regression Analysis for variables predicting PDI scores at 24 months of age (*N*=67)

Variable	*B±SE B*	Standardized regression coefficients (β)
Benzodiazepine use (yes)[a]	-10.48±3.77	-.34**
ISSI-SF Total Score (4mths)	0.18±0.24	.09
Total HOME score (24mths)	1.50±0.46	.40**
Group		
Control	0	
Buprenorphine	1.80±3.62	.06
Methadone	-1.33±4.36	-.04

Note. For the regression model as a whole, R^2=.31, $F(5,61)$ = 5.42, *p*<.001.

p<.05, ** *p*<.01, ***p*<.001

[a] Self-reported use during pregnancy.

Table 6.7 Multiple Regression Analysis for variables predicting BRS scores at 24 months of age (*N*=61)

Variable	$B \pm SE\ B$	Standardized regression coefficients (β)
ISSI-SF Total Score (4mths)	0.21±0.17	.17
Total HOME score (24mths)	0.87±0.38	.33*
Group		
Control	0	
Buprenorphine	2.61±3.00	.14
Methadone	-2.12±3.30	-.08

Note. For the regression model as a whole, R^2=.15, F(4,56) = 2.56, *p*<.05.

B±SE B reported in terms of the original distributions; however β, R^2 & *F* values reported in terms of the transformed data (power 2.5 transformation). *p*<.05.
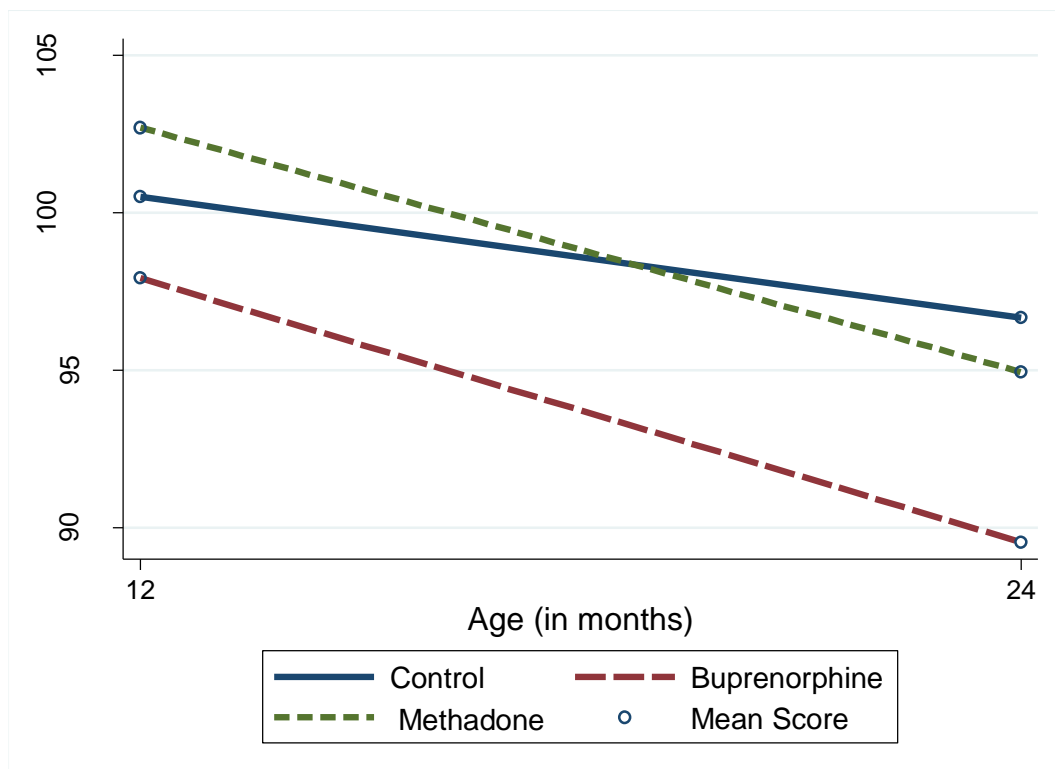
Figure 6.1 Mean MDI scores for each group at the 12- and 24-month follow-up assessment.
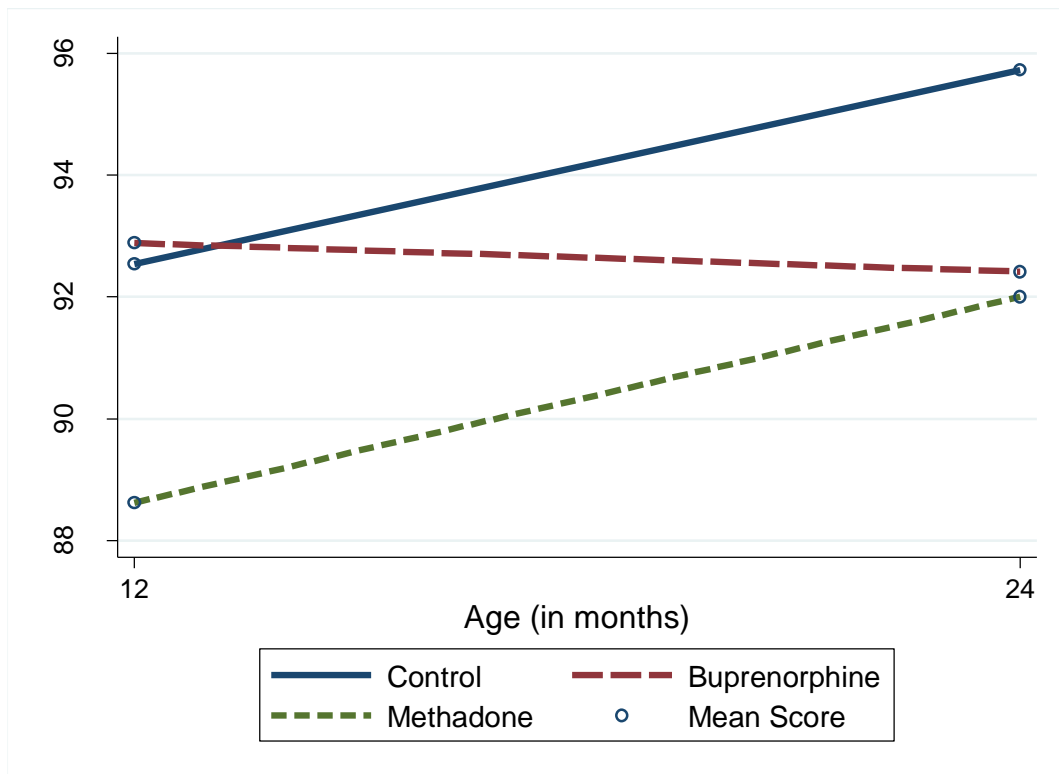
Figure 6.2 Mean PDI scores for each group at the 12- and 24-month follow-up assessment.
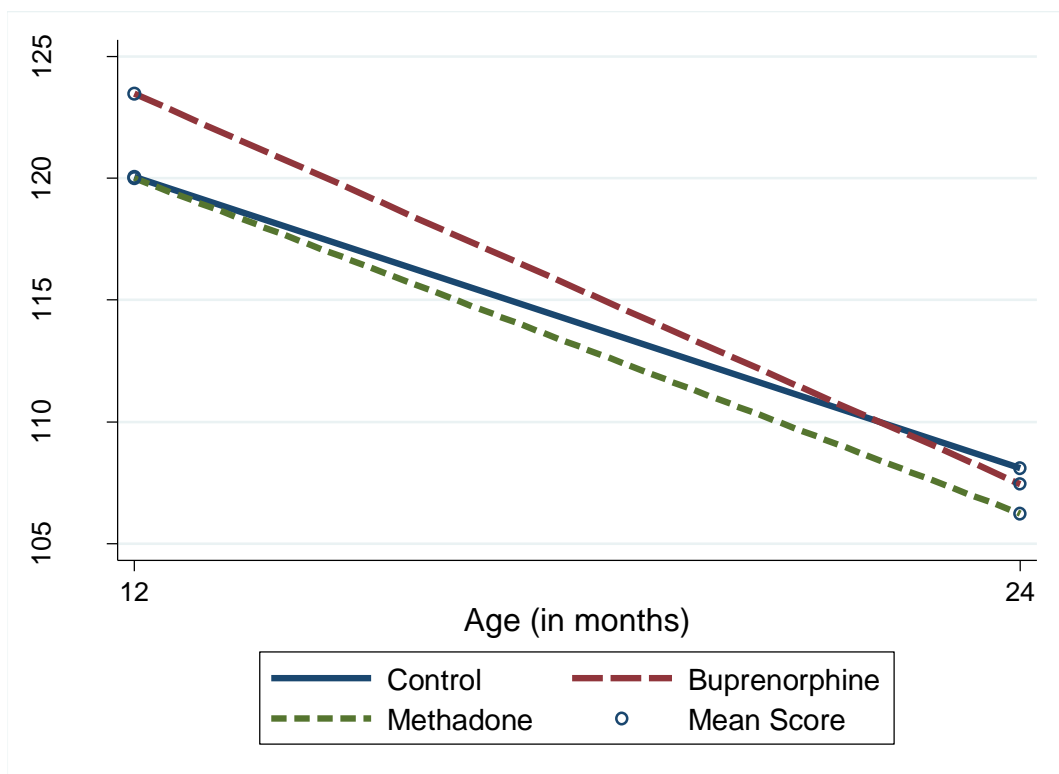
Figure 6.3 Mean BRS scores for each group at 12- and 24-month follow-up assessment.

Table 7.1 Factor scores and Easy/Difficult Scale scores of the Short Temperament Scale for

Infants, at 4 months of age, by group

Temperament Scores	Control (n=33)	Buprenorphine (*n*=29)[a]	Methadone (*n*=24)	*p*
Factor Scores				
Approach	1.71 (1.00-3.71)	1.71 (1.00-2.71)	1.86 (1.00-3.43)	.80
Rhythmicity	2.67(1.00-4.00)	2.33 (1.67-4.00)	2.00 (1.17-3.67)	.16
Cooperation/Manageability [b]	2.33±0.60	2.30±0.65	2.14±0.56	.48
Activity/Reactivity	4.25±0.81	4.03±0.90	4.12±0.80	.58
Irritability[b]	2.51±0.94	2.41±0.59	2.52±1.12	.97
Easy/Difficult Scale Score[c]	2.24±0.57	2.15±0.41	2.19±0.63	.85

Note. Higher scores reflect more difficult temperament (e.g. greater distractibility, lower persistence). Values reported as *M±SD* or median (range). *M±SD* reported in terms of the original distributions; however where data has been transformed, reported *p*-values are for the transformed distributions.

[a] Data missing for one BM child

[b] Power 0.4 transformation.

[c] Square root transformation.

Table 7.2 Multiple Regression Analysis for variables predicting Easy/Difficult Scale scores at four months of age (*N*=85)

Predictor Variables	*B±SE B*	Standardised regression coefficients (β)
Global Attachment Score[a]	-0.04±0.01	-.43***
GHQ Total Score[a]	0.03±0.01	.29**
ISSI-SF Total Score[a]	0.00±0.01	.03
Group		
Control	0	
Buprenorphine	-0.07±0.12	-.06
Methadone	0.06±0.13	.05

Note. For the regression model as a whole, R^2=.32, F(5,79)=7.50, *p*<.0001.

p<.05, ** *p*<.01, ***p*<.001, †*p*<.0001.

[a] Global attachment, GHQ and ISSI-SF scores measured at four month follow-up assessment.

Table 7.3 Factor scores and Easy/Difficult Scale scores of the Short Temperament Scale for Toddlers, at 12 months of age, by group

Temperament Scores	Control (*n*=33)	Buprenorphine (*n*=28)	Methadone (*n*=22)	*p*
Factor Scores				
Approach/ Adaptability	3.00 (2.20-4.80)	3.00 (2.00-5.25)	3.00 (2.20-4.20)	.64
Reactivity	3.79±0.63	3.51±0.69	3.71±0.59	.23
Persistence	2.93±0.77	2.99±0.91	2.61±0.80	.24
Cooperation/Manageability	3.42±0.94	3.63±0.90	3.53±0.97	.69
Distractibility	3.90±0.58	4.16±0.79	3.90±0.69	.27
Rhythmicity	2.57±0.62	2.74±0.92	2.80±0.68	.50
Easy/Difficult Scale Score[a]	3.49±0.50	3.41±0.58	3.42±0.48	.78

Note. Higher scores reflect more difficult temperament (e.g. greater distractibility, lower persistence). Values reported as median (range) or *M±SD*. *M±SD* reported in terms of the original distributions; however where data has been transformed, reported *p*-values are for the transformed distributions.

[a] Log transformation.

Table 7.4 Multiple Regression Analysis for variables predicting Easy/Difficult Scale scores at 12 months of age (*N*=82)

Predictor Variables	*B±SE B*	Standardised regression coefficients (β)
Global Attachment Score[a]	-0.03±0.01	-.32**
Group		
Control	0	
Buprenorphine	-0.05±0.13	-.04
Methadone	0.03±0.14	.03

Note. For the regression model as a whole, R^2=.10, F(3,78)=3.05, *p*<.05.

p<.05, ** *p*<.01, ***p*<.001, †*p*<.0001

[a] Global attachment scores from the Maternal Postnatal Attachment Scale measured at four month follow-up assessment.

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

Temperament Scores	Control (*n*=30)	Buprenorphine (*n*=23)	Methadone (*n*=18)	*p*
Factor Scores				
Approach/ Adaptability	3.42±0.70	3.47±0.66	3.10±0.57	.16
Reactivity	3.80±0.64	3.75±0.61	3.87±0.82	.86
Persistence	2.73±0.74	2.78±0.91	2.38±0.67	.22
Cooperation/Manageability	3.20 (1.80-4.40)	3.25 (2.00-4.40)	3.10 (2.00-4.60)	.99
Distractibility	4.08±0.59	3.91±0.70	3.77±0.58	.24
Rhythmicity	2.61±0.73	2.84±0.59	3.04±0.84	.13
Easy/Difficult Scale Score[a]	3.48±0.49	3.47±0.44	3.40±0.56	.81

Note. Higher scores reflect more difficult temperament (e.g. greater distractibility, lower persistence). †Values reported as *M±SD* or median (range). *M±SD* reported in terms of the original distributions; however where data has been transformed, reported *p*-values are for the transformed distributions.

[a] square root transformation.

Table 7.6 Multiple Regression Analysis for variables predicting Easy/Difficult Scale scores at 24 months of age (*N*=70)

Predictor Variables	*B*±*SE B*	Standardised regression coefficients (β)
Global Attachment Score[a]	-0.03±0.01	-.27*
ISSI-SF Total Score[a]	-0.01±0.01	-.20
Group		
Control	0	
Buprenorphine	-0.07±0.13	-.08
Methadone	-0.08±0.15	-.06

Note. For the regression model as a whole, R^2=.15, $F(4,65)$=2.86, $p<.05$.

B±*SE B* reported in terms of the original distributions; however β, R^2 & *F* values reported in terms of the transformed (squared) data. *$p<.05$, ** $p<.01$, ***$p<.001$, †$p<.0001$

[a] Global attachment and ISSI-SF scores measured at four month follow-up assessment.
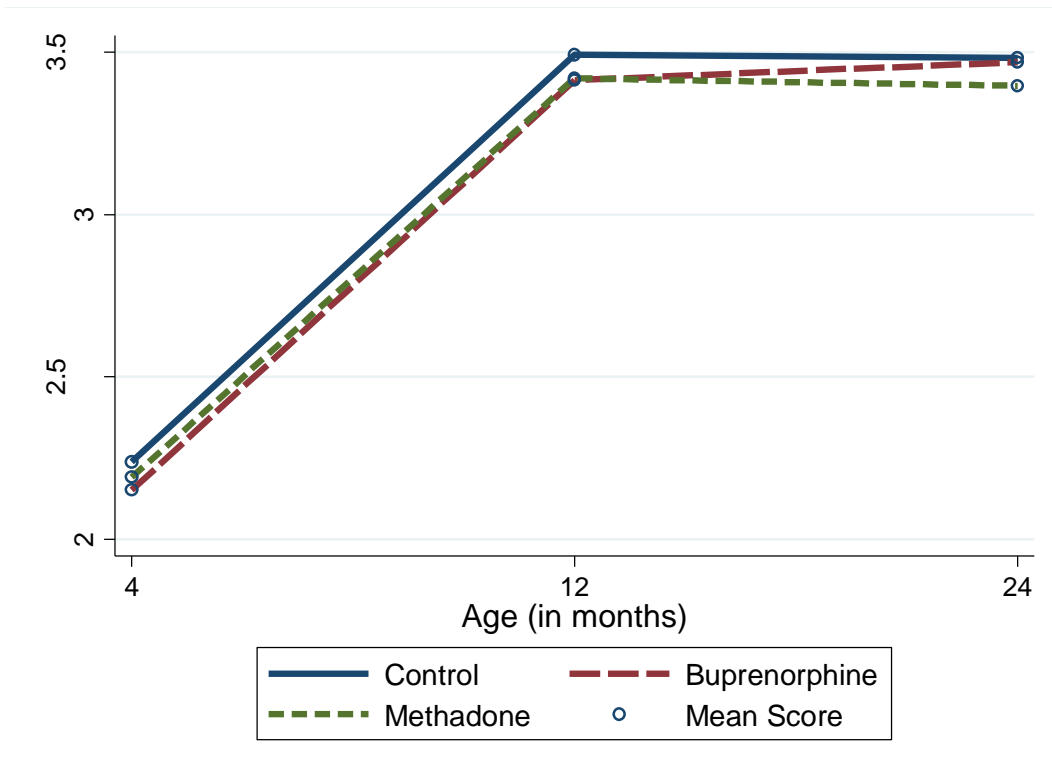
Figure 7.1 Mean EDS raw scores for each group at the 4-, 12- and 24-month follow-up assessments.
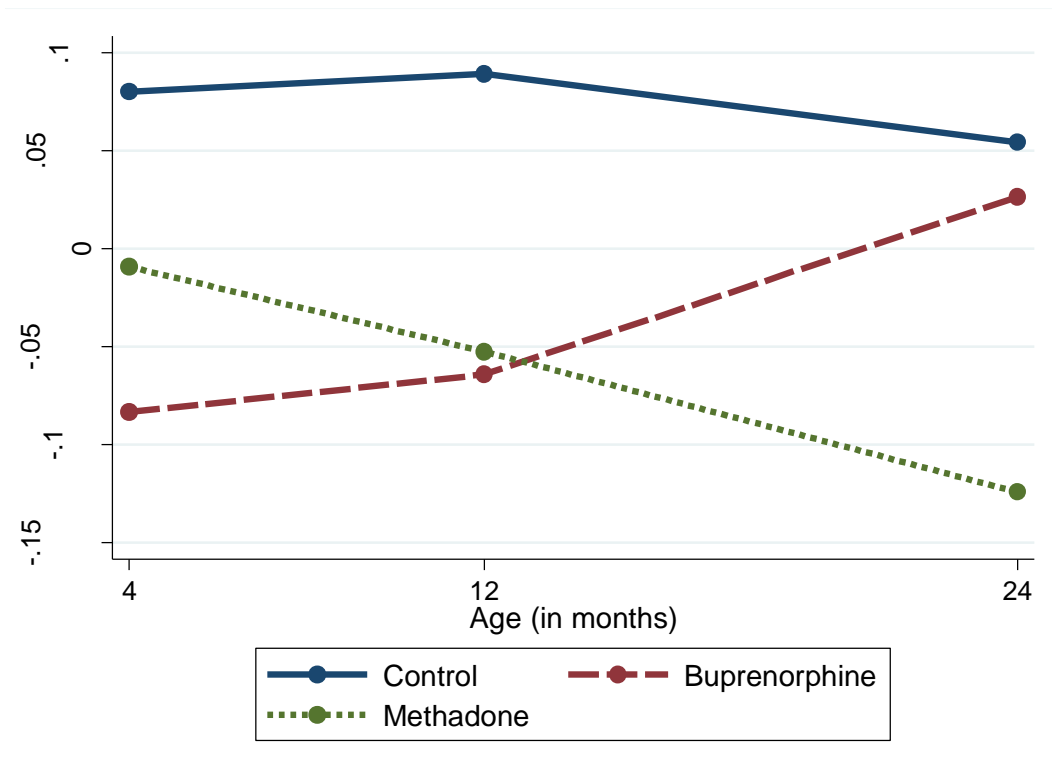
Figure 7.2 Mean EDS z-scores for each group at the 4-, 12- and 24-month follow-up assessments.

Appendices

Appendix A. Screening Questionnaire

BUPRENORPHINE AND METHADONE IN PREGNANCY: EFFECTS ON THE MOTHER AND FETUS/NEONATE

Screening Survey

If all bolded boxes are ticked then the subject is eligible for the study. The **"yes"** box in the **"Suitable for research study"** row must then be ticked and you must sign and date below the survey.

Subject initials: ☐☐☐

Are you aged between 16 and 40 years?	**Yes** ☐	No ☐
Is your gestational age ≤28 weeks?	**Yes** ☐	No ☐
Are you expecting twins?	Yes ☐	**No** ☐
Are you participating in another research study?	Yes ☐	**No** ☐
Do you consume more than 7 standard alcoholic drinks in an average week?	Yes ☐	**No** ☐
Are you taking any medication for HIV or epilepsy	Yes ☐	**No** ☐

Suitable for research study	**Yes** ☐	No ☐

Investigator Signature: …………………… Date: ………………………

Appendix B. Information Sheet for Maintenance Group Participants

Study Title: Child Health and Development Study
(Buprenorphine and methadone in pregnancy: Effects on mother, foetus/ neonate and child.)

Methadone is recognised as being very beneficial in the treatment of heroin dependence, but for pregnant women there is a risk of Neonatal Abstinence Syndrome (NAS). The developing child becomes dependent on the methadone in the mother's circulation and then experiences withdrawal following birth. Symptoms of NAS may be mild and include excessive crying, poor sleep and feeding, excessive yawning and sneezing, but may be severe with development of fever, diarrhoea and seizures. It is unclear why some babies suffer more severe symptoms while others have mild symptoms or do not develop this syndrome at all.

Buprenorphine (Subutex) is now being used widely in the treatment of heroin dependence and is known to produce milder physical dependence and fewer withdrawal symptoms than methadone. However; it is has not been approved as a maintenance treatment in pregnant women. A number of studies have reported that babies born to women who were maintained on buprenorphine during pregnancy had very few symptoms of NAS or did not develop NAS at all. **You should be aware that while existing studies suggest that buprenorphine is as safe as methadone during pregnancy, there have been no large-scale studies performed and therefore, the safety and effectiveness of this drug have not been firmly determined in this population of patients. Studies previously undertaken have also not directly compared the effects of buprenorphine on the mother and the baby with the effects of methadone. In addition, no long-term studies of children exposed to buprenorphine during pregnancy have been done.**

The first aim of this study is to determine the extent to which the NAS occurs with mothers who are maintained on buprenorphine during pregnancy. This study will also look at safety and effectiveness of buprenorphine in comparison with methadone during pregnancy. The second aim of the study is to assess the physical and intellectual development of children from birth up to the age of three years.

To be eligible to take part in the project, you will need to
   a) be between 16 and 40 years of age
   b) have a gestational age of up to 28 weeks
   c) be either requesting an opioid maintenance treatment or be currently enrolled in a methadone or buprenorphine program
   d) cooperate with study procedures
   e) not have major psychiatric illness
   f) not have twin pregnancy

Your eligibility to participate in this study will be confirmed by the research medical staff during this visit.

If you are already on a methadone or buprenorphine program and eligible to enrol in the study, you will continue on this maintenance therapy throughout your pregnancy and thereafter. If you are not considered eligible to enrol in the study, you will receive standard clinical treatment.
If you are currently requesting maintenance treatment and are eligible to participate in the study, you will be offered a choice of methadone or buprenorphine maintenance treatment. If

you are not eligible to enrol, you will be routinely inducted on methadone and receive standard clinical treatment.

You will be able to continue your maintenance medication after the birth of the baby, including during breastfeeding.

You will receive standard gynaecological and obstetrical care during your pregnancy that will not be affected by your participation in this study. However, if you are to be involved in this study, **it is essential that you accurately attend all the routine pregnancy checkups**.

What you will need to do during your pregnancy and after the birth of your baby
Aside from the normal medical care involved with routine pregnancy checkups, which are essential to attend if you are to be involved in this study, you will be required to attend 3 additional outpatient visits, complete a number of questionnaires and supply a number of urine and blood samples during pregnancy (antenatally) and in the first month of the birth of the baby (postnatally). These requirements are outlined in the attached study timetable.

In particular, you will also be asked to do the following:
- record the exact time of taking your maintenance drug on the day you visit the outpatient clinic
- complete the following questionnaires (this should take only 10 minutes for all) when visiting the clinic:
  1) Short Opioid Withdrawal Scale
  2) Visual analogue scale assessing positive effects of opioids
  3) Use of other drugs
  4) Adverse effects

You will also be asked to complete these questionnaires once a week during the first 4 weeks after birth. After you have been discharged from the hospital you will be visited once a week by research staff who will collect the questionnaires.

What additional tests you will have during your pregnancy and after the birth of your baby
Aside from the normal medical tests that will be performed during pregnancy and after delivery, this study will require you to supply the following samples:
I. Antenatal samples
- 2 (or up to 4 if you are Hep C positive) additional blood samples, of 5 ml each, will be taken for laboratory analyses to assess your liver and kidney function and will be performed up on recruitment and once more during pregnancy.
- 4-6 random urine samples throughout your pregnancy depending on the gestational age at your first visit. These samples will be tested for a number of licit and illicit drugs and are strictly for the purposes of this study only. The results will not exclude you from the study or affect your medical care and will be kept confidential. We do however ask that you not take illicit drugs while participating in this study.
- 4-6 blood samples will be taken on the same days as your random urine samples to assess the concentration of your maintenance drug and other drugs if present. Blood samples will be 8 ml each.

II. At delivery
- 1 blood sample (3ml) will be taken from you to determine the concentration of the maintenance drug in your blood.
- 1 blood sample (in addition to one routine sample) will be taken from the umbilical cord after delivery to assess how much of the maintenance drug has crossed the placenta and reached the baby.

III. Postnatal samples

- 2 samples of breast milk will be taken (on postnatal day 3 by the hospital nurses and in week 2 post delivery by research staff at a home visit) to estimate how much of the maintenance drug is present in the breast milk.
- 2 blood samples will be taken at the same time as the breast milk samples [i.e. on day 3 (3 ml) and in the second week post delivery (8ml)] to determine the concentration of the maintenance drug in your blood and compare this with the concentration in the breast milk. You will be required to record the time of taking your maintenance medication on these days.
- 2 blood samples (3 ml each) will be taken once a week in weeks 3 and 4 post delivery by a research staff member at a home visit to determine whether there are any changes in the concentration of the maintenance drug as your body returns back to the pre-pregnancy condition
- 1 (final!) urine sample will be collected from you on one of the home visits for the purpose of drug use monitoring.

What information we will collect from your and your baby's case notes

For the purpose of the study we will be collecting the following information from your Pregnancy Hand-Held Record: significant history factors, past pregnancies, medical examination, due date, laboratory tests, maintenance drug dose, scans, pregnancy problems (if any arise), pregnancy progress notes. Following the delivery we will collect the following information from your case notes: any obstetric complications during labour, baby's condition during labour, duration of labour, mode of delivery, and pain management. From you baby's case notes we will collect information on the baby's condition at birth. Your baby will receive standard care and treatment (if necessary) prescribed by the hospital's paediatricians. All information will be secured and kept confidential. **This study will not influence in any way your or your baby's routine treatment.**

Assessment of Neonatal Abstinence Syndrome

One of the most important aims of this study is to assess whether your newborn baby has signs of opioid withdrawal, using the Neonatal Abstinence Scale. This Scale is a list of withdrawal signs with an accurate scoring system. It is a non-invasive, routinely administered survey performed by the hospital nurses, usually with the mother's help. The baby's condition is normally assessed every 4 hours (if awake) while in the hospital. In the first week of discharge from the hospital the scale will be administered at the hospital during your baby's routine visit to a paediatrician. In the remaining weeks (until the 4th week from the birth of your baby) this will be performed by trained research staff at home visits. This follow up is necessary because sometimes this syndrome reoccurs or presents late, between 2 and 4 weeks of age.

Following up of your child

Because methadone and other opiate drugs have the potential to cause some long-lasting effects on the physical and intellectual development of children, we would like to invite you to participate in the follow-up part of this study. This will give you the opportunity to have your child assessed in terms of his or her physical and intellectual functioning each year until they are 3 years old. This part of the study will be done with one visit back to the Women's and Children's Hospital at 4 months of age and then by visits to your home by our research assistant once a year until your child is 3.

4 Month Visit at the Hospital

When your baby is 4 months of age we will invite you to an appointment at the Women's and Children's Hospital.   We will pay for taxis or car parking necessary for you to attend this visit. Because at this young age it is difficult to test children's intellectual functioning, we can do this indirectly by assessing how well their vision is developing. This is called Visual Evoked Potential

(VEP) testing and involves having your baby look at a series of checkerboard patterns on a computer screen. Three small sensors will be attached with gel to your baby's head in order to detect nerve signals. VEP assessment takes about 20 minutes to do and is a procedure done frequently at the hospital. Babies cope very well with this test. Your baby's length, head size and weight will also be measured. At this visit we will ask you to complete a short questionnaire. This questionnaire focuses on the health of your baby, the personality of your baby and sleeping patterns of your baby. It will also ask about your health, your family situation and the social supports available to you. We expect this visit will take no longer than 1 to 1.5 hours in total.

A Visit Once a Year to your Home
Once a year for three years you will be visited at home by one of our trained research assistants. During this visit your child's development will be assessed and you will be provided with direct feedback about how your child is going. We will ask you again about the health of your baby/toddler, the personality of your baby/toddler and sleeping patterns of your baby/toddler. We will ask some questions about your child's household environment and repeat some of the questions about your family situation and the social supports available to you. We expect this visit to take no longer than 1.5 to 2 hours. At the final home visit (when your child is three years of age) we will also ask you complete a short questionnaire about your child's language development. At this age children's receptive and expressive language skills are rapidly progressing and are important for successful learning.

In addition to the home visit when your child is three, you will again be invited to attend an appointment at the Women's and Children's Hospital for a follow-up assessment of your child's visual development. At this time the VEP testing will be repeated and we will weigh and measure your child. We expect this visit to take no longer than 30 to 45 minutes. We will pay for taxis or car parking necessary for you to attend this visit.

If at any time during the follow-up part of the study your child appears to be having problems with their development or has any other health issues about which you are concerned we would be very happy to offer help or advice about services.

Confidentiality
All information that you provide in this study will be kept confidential at all times. For the purpose of this study you will be assigned a code instead of your name in order to prevent you from being identified in any way. The only exception to this is the legal requirement to pass on information about child abuse or neglect to CYFS (formerly FAYS). If you wish to know what was found at the end of the project we will be happy to provide a summary of the results on your request. You won't need to identify yourself for this purpose. In the event that we have trouble contacting you during the study (e.g. you change house or telephone number) we will attempt to contact you via the Central Register of Methadone Prescribing (DASC) in order to check whether you still wish to be part of the study. We would also like to collect the name and contact details of a friend or relative who would know how to get in contact with you.

Leaving the study
If you decide to withdraw from this study for any reason you may do so at any time without having to give a reason to anyone. If you decide not to participate in this study or you withdraw, you may do this freely without affecting your or your or your child's medical care at the Women's and Children's Hospital in any way.

Effects, side effects and inconvenience of the study procedures

Blood samples will be collected through a needle prick that may cause temporary pain. There is slight risk of bruising at the site of the prick, but this risk will be reduced because we use only qualified people to do the procedures. The total volume of blood to be collected for the purpose of the study from women in the buprenorphine or methadone maintenance groups is 72-98 ml on 11 occasions over a period of 4 - 7 months, depending on the gestational age at the time of enrolment. The maximum blood volume taken at one visit will be 13 ml [if both drug concentration (8ml, random) and liver/kidney function samples (5ml) are taken on the same occasion]. This is unlikely to affect your or your baby's health.

Both buprenorphine and methadone may cause a number of adverse effects.

      a. Buprenorphine: Like other opioids it may cause cardiac, respiratory and central nervous system depression and decrease in blood pressure. It may also cause some increase in liver enzymes. Most common adverse effects that develop in 5% of patients are similar to other opioids and include: constipation and opioid withdrawal symptoms such as abdominal pain, back pain, chills, fever, headache, upset stomach, insomnia, runny nose, sweating, fatigue.

      b. Methadone: The major adverse effect of methadone is respiratory depression. Other reported events are also similar to other opioids and include nausea, vomiting, constipation, dizziness, drowsiness, light-headedness, dry mouth, sweating and confusion. Less common are: a decrease or increase in heart rate, palpitations, blurred vision, stomach cramps or pain.

If you have been using methadone or buprenorphine, you are already familiar with these possible adverse effects of these drugs. If you are new to maintenance treatment you may experience some of these effects.

Compensation/Indemnity

If you, as a participant of this research, suffer injury, compensation may, at the discretion of the researcher or sponsor of the research, be paid without litigation. However, compensation is not automatic and you may have to take legal action in order to receive payment.

Payment/Cost

To compensate you for any inconvenience you experience as a result of this study you will be paid **$350** in total for completion of the study. This will be paid in $50 instalments throughout the study. You will receive 2 instalments during your pregnancy, 1 instalment after the birth of your baby, 1 instalment when your baby is 4 months old and an instalment at each yearly visit until your child is 3 years old (7 instalments in total). Any additional tests involved in this study that are outside your routine medical checkups will be conducted at no cost to you. As a special thank you to your baby/child for their involvement, they will receive a small gift at each visit, beginning when they are 4 months of age. **We will also pay for a taxi or car-parking fees when you come for additional visits including the 4 month follow-up visit to the hospital**.

Study timetable for maintenance subjects

Time	Record exact time of maintenance dose Routine Visit	Questionnaires	Maternal Urine Samples	Maternal Blood Samples		Cord Blood Sample	Breast Milk Sample	Finnegan Scale
				Drug concentrations	Liver and kidney function			
Antenatal	Screening and consent form collection will occur on the first antenatal visit							
Up to week 11	X At any routine visit	X	3 random urine samples	3 blood samples taken on the day of the urine sample	1 blood sample at enrolment			
Week 12	X	X						
Week 16	X	X						
Week 18	X	X						
Week 22		X						
Week 26		X						
Week 28	X	X						
Week 30		X	3 random urine samples	3 blood samples taken on the day of the urine sample				
Week 32	X	X			X			
Week 34	X	X						
Week 36	X	X						
Week 37	X	X						
Week 38	X	X						
Week 39	X	X						
Week 40	X	X						
Delivery				X		X		
Postnatal								
Week 1	X	X	1 random urine sample	X			X Day 3	X 4-hourly until discharge
Week 2	X	X		X			X	X
Week 3		X		X				X
Week 4		X		X				X
4 Months		X	Visit to the hospital to assess Visual Evoked Potential of your baby					
1 Year		X	Visit to your home to assess the development of your child					
2 Years		X	Visit to your home to assess the development of your child					
3 Years		X	Visit to your home to assess the development of your child					

Questionnaires to be completed:
Structured initial interview (first visit only)
Clinical opioid withdrawal scale (administered by medical/research staff)

Subjective opioid withdrawal scale, Visual scale of opioid effect, Other drug use/co-medication questionnaire (all self-report), Adverse effects questionnaire (monthly self-report)

From 4 months to 3 years of age: questionnaire to assess your child's development, your household environment and your current family situation.

If at any time you wish to contact the project team, please ring:

Pregnancy and the Neonatal Period
- Ms Justine Whitham (Tel:).
- Dr Olga Lopatko (Tel:).

Follow-up of Your Child
- Dr Nicola Spurrier (Tel:).
- Ms Justine Whitham (Tel:).

This study has been reviewed by the Women's and Children's Hospital Research Ethics Committee. Should you wish to discuss the study with someone not directly involved, in particular in relating to matters concerning policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Research Coordinator at the Women's and Children's Hospital, Ms Brenda Penny (Tel:).

Appendix C. Consent Form for Maintenance Group Participants

Study Title: Buprenorphine and methadone in pregnancy: Effects on the developing infant and child.

1. I . . . . (please print) hereby consent to take part in the research project entitled **"***Buprenorphine and methadone in pregnancy: Effects on the developing infant and child***."** I have read the Information Sheet and understood its contents. I have had the nature and purpose of the research project, so far as it affects me, fully explained to my satisfaction by the research worker. My consent is freely given.

2. I understand that I may not directly derive any clinical benefit from taking part in the research project.

3. I acknowledge that the details of the following procedures, including possible risks and or side effects, discomforts and inconveniences have been explained to me
   - Collection of blood and urine samples from myself
   - Visual Evoked Potential assessment of my infant at 4 months of age
   - Developmental assessments of my infant/child at 12, 24 and 36 months of age

4. I understand that while information gained during the research project may be published, I will not be identified and my personal results will remain confidential.

5. I understand that I may withdraw from the research project at any stage, without giving a reason, and that this will not affect my medical care, now or in the future.

6. I understand the statement concerning payment, which is contained in the Information Sheet.

7. I have had the opportunity to discuss taking part in the research project with a family member or friend.

8. I consent to my contact details being accessed from the Central Register of Methadone Prescribing in the rare event that I cannot be contacted by any other means.

9. I am aware that I should retain a copy of this Consent Form, when completed, and the information sheet.

Signed . . . .   Date . . . .

Witness Signature . . . .   Date . . . .

       Name . . . .

I . . . .   certify that I have explained the nature and procedures of the research

project to . . . .   and consider that he/she understands what is involved.

Signed . . . .   Date . . . .

Status in Project   . . . .

Appendix D. Consent Form for Infant Participation

Buprenorphine and methadone in pregnancy: Effects the developing infant and child

1. I . . . . (please print) hereby consent for my child . . . . (please print) to take part in the research project entitled **"***Buprenorphine and methadone in pregnancy: Effects on developing infant and child***."** I have read the Information Sheet on their behalf and understood its contents. I have had the nature and purpose of the research project, so far as it affects my child, fully explained to my satisfaction by the research worker. My consent for my child is freely given.

2. I understand that my child may not directly derive any clinical benefit from taking part in the research project.

3. I acknowledge that the details of the following procedures, including possible risks and or side effects, discomforts and inconveniences have been explained to me
   - Visual Evoked Potential assessment at 4 months of age
   - Developmental assessments at 12, 24 and 36 months of age

4. I understand that the research staff have a legal obligation to pass on information about child abuse or neglect to Child Youth and Family Services (formerly FAYS).

5. I understand that while information gained during the research project may be published, my child will not be identified and their personal results will remain confidential.

6. I understand that I may withdraw my child from the research project at any stage, without giving a reason, and that this will not affect their medical care, now or in the future.

7. I have had the opportunity to discuss my child taking part in the research project with a family member or friend.

8. I am aware that I should retain a copy of this Consent Form, when completed, and the information sheet.

Signed . . . .   Date . . . .

Witness Signature . . . .   Date . . . .

       Name . . . .

I . . . . certify that I have explained the nature and procedures of the research

project to . . . . and consider that he/she understands what is involved.

Signed . . . .   Date . . . .

Status in Project . . . .

Appendix E. Information Sheet for Control Group Participants

Study Title: Child Health and Development Study
(Buprenorphine and methadone in pregnancy: Effects on mother, foetus/ neonate and child.)

Methadone is recognised as being very beneficial in the treatment of heroin dependence, but for pregnant women there is a risk of Neonatal Abstinence Syndrome (NAS). The developing child becomes dependent on the methadone in the mother's circulation and then experiences withdrawal following birth. Symptoms of NAS may be mild and include excessive crying, poor sleep and feeding, excessive yawning and sneezing, but may be severe with development of fever, diarrhoea and seizures. It is unclear why some babies suffer more severe symptoms while others have mild symptoms or do not develop this syndrome at all.

Buprenorphine is now being used for treatment of heroin dependence, however little is known of its effects during pregnancy and the effect on the unborn child. The aim of this study is to determine the extent to which NAS occurs, if at all, with mothers who are maintained on buprenorphine. It has been suggested that babies born to women who are maintained on buprenorphine compared to methadone will display very few symptoms of NAS or will present as normal healthy babies with no symptoms at all. This study will look at the safety and effectiveness of buprenorphine in comparison with methadone during pregnancy. We would also like to assess the physical and intellectual development of children up to the age of three to be absolutely sure that buprenorphine is a safe drug to use during pregnancy.

For this project we require normal healthy control subjects who are not participating in opioid maintenance treatments and do not use opioids (drugs and medications like heroin, morphine and codeine) on a regular basis. This is a research project, and you can choose whether or not you would like to be involved. If you choose not to be involved, there will be no effect on your medical care.

To be eligible to take part in the project, you will need to
  g) be between 16 and 40 years of age
  h) have a gestational age of up to 28 weeks
  i) not be using opioids (drugs and medications like heroin, morphine, methadone or codeine) on a regular basis
  j) cooperate with study procedures
  k) not have major psychiatric illness
  l) not have twin pregnancy

Your eligibility to participate in this study will be confirmed by the research medical staff during this visit.

What you will need to do during your pregnancy and after the birth of your baby
Aside from the normal medical care involved with routine pregnancy checkups, which are essential to attend if you are to be involved in this study, you will be required to attend 3 additional outpatient visits, complete a questionnaire and supply a number of urine and blood samples during pregnancy. These requirements are outlined in the attached study timetable.

In particular when visiting the clinic, you will also be asked to complete questionnaires on what drugs and medications you have used and how you have been feeling since your previous visit (this should take only 5-10 minutes).

What additional tests you will have during this study

Aside from the normal medical tests that will be performed during pregnancy and after delivery this study will require you to supply the following samples:

- 2 (or up to 4 if you are Hepatitis C positive) additional blood samples, of 5 ml each, will be taken for laboratory analyses to assess your liver and kidney function and will be performed upon recruitment and once more during pregnancy.
- 4-6 random blood and urine samples throughout your pregnancy, depending on the gestational age at your first visit, and one random blood and urine sample in the postnatal period. These samples will be tested for a number of licit and illicit drugs and are strictly for the purposes of this study only. The results will not exclude you from the study or affect your medical care and will be kept strictly confidential. We do however ask that you not take illicit drugs while participating in this study. Blood samples will be 5 ml each. Together with blood collected for your liver and kidney function tests this will add up to 40-60 ml of blood over the 3.5-6 months period and will not affect your or your baby's health.

What information we will collect from your and your baby's case notes

For the purpose of the study we will be collecting the following information from your Pregnancy Hand-Held Record: significant history factors, past pregnancies, medical examination, due date, laboratory tests, scans, pregnancy problems (if any arise), pregnancy progress notes. Following the delivery we will collect the following information from your case notes: any obstetric complications during labour, baby's condition during labour, duration of labour, mode of delivery, and pain management. From your baby's case notes we will collect information on the baby's condition at birth. Your baby will receive standard care and treatment (if necessary) prescribed by the hospital's paediatricians. All information will be secured and kept confidential. **This study will not influence in any way your or your baby's routine treatment.**

Assessment of Neonatal Abstinence Syndrome

One of the most important aims of this study is to assess whether newborn babies whose mothers have been on the maintenance treatment for opioid dependence develop signs and symptoms that are not developed by other babies. To assess this we will be using the Neonatal Abstinence Scale. This Scale is a list of signs that are characteristic of withdrawal with an accurate scoring system. It is a non-invasive, routinely administered survey performed by the hospital nurses, usually with the mother's help. The baby's condition is normally assessed every 4 hours (if awake) while in the hospital. Following your baby's discharge form the hospital the scale will be administered by trained research staff at home visits once a week for 3 weeks. This follow up is necessary because sometimes this syndrome reoccurs or presents late, between 2 and 4 weeks of age. While this syndrome is unlikely to develop in your baby, it is important that we compare those babies that were born to mothers on opioid maintenance treatment with babies whose mothers did not use opioids during pregnancy, as some of the signs (e.g. crying) occur in normal babies.

Follow up of your child

Because methadone and other opiate drugs have the potential to cause some long-lasting effects on the physical and intellectual development of children, we would like to follow the development of all children to the age of three years. This will give you the opportunity to have your child assessed in terms of his or her physical and intellectual functioning each year until they are 3 years old. This part of the study will be done with one visit back to the Women's and Children's Hospital at 4 months of age and then by visits to your home by our research assistant once a year until your child is 3.

4 Month Visit at the Hospital

When your baby is 4 months of age we will invite you to an appointment at the Women's and Children's Hospital.   We will pay for taxis or car parking necessary for you to attend this visit. Because at this young age it is difficult to test children's intellectual functioning, we can do this indirectly by assessing how well their vision is developing. This is called Visual Evoked Potential (VEP) testing and involves having your baby look at a series of checkerboard patterns on a computer screen. Three small sensors will be attached with gel to your baby's head in order to detect nerve signals. VEP assessment takes about 20 minutes to do and is a procedure done frequently at the hospital. Babies cope very well with this test. Your baby's length, head size and weight will also be measured. At this visit we will ask you to complete a short questionnaire. This questionnaire focuses on the health of your baby, the personality of your baby and sleeping patterns of your baby. It will also ask about your health, your family situation and the social supports available to you. We expect this visit will take no longer than 1 to 1.5 hours in total.

A Visit Once a Year to your Home
Once a year for three years you will be visited at home by one of our trained research assistants. During this visit your child's development will be assessed and you will be provided with direct feedback about how your child is going. We will ask you again about the health of your baby/toddler, the personality of your baby/toddler and sleeping patterns of your baby/toddler. We will ask some questions about your child's household environment and repeat some of the questions about your family situation and the social supports available to you. We expect this visit to take no longer than 1.5 to 2 hours. At the final home visit (when your child is three years of age) we will also ask you complete a short questionnaire about your child's language development. At this age children's receptive and expressive language skills are rapidly progressing and are important for successful learning.

In addition to the home visit when your child is three, you will again be invited to attend an appointment at the Women's and Children's Hospital for a follow-up assessment of your child's visual development. At this time the VEP testing will be repeated and we will weigh and measure your child. We expect this visit to take no longer than 30 to 45 minutes. We will pay for taxis or car parking necessary for you to attend this visit.
If at any time during the follow-up part of the study your child appears to be having problems with their development or has any other health issues about which you are concerned we would be very happy to offer help or advice about services.

Confidentiality
All information that you provide in this study will be kept confidential at all times. For the purpose of this study you will be assigned a code instead of your name in order to prevent you from being identified in any way. The only exception to this is the legal requirement to pass on information about child abuse or neglect to CYFS (formerly FAYS). If you wish to know what was found at the end of the project, we will be happy to provide a summary of the results on your request. You won't need to identify yourself for this purpose. In the event that we have trouble contacting you during the study (e.g. you change house or telephone number) we would like to collect the name and contact details of a friend or relative who would know how to get in contact with you.

Leaving the study
If you decide to withdraw from this study for any reason you may do so at any time without having to give a reason to anyone. If you decide not to participate in this study or you withdraw, you may do this freely without affecting your or your or your child's medical care at the Women's and Children's Hospital in any way.

Effects, side effects and inconvenience of the study procedures

Blood samples will be collected through a needle prick that may cause temporary pain. There is slight risk of bruising at the site of the prick, but this risk will be reduced because we use only qualified people to do the procedures.

The total maximum volume of blood to be collected 40-60 ml of blood on a maximum of 7 occasions over the 3- 6 months period, depending on the gestational age at the time of enrolment. The maximum blood volume taken at one visit will be 10 ml [if both drug concentration (5ml, random) and liver/kidney function samples (5ml) are taken on the same occasion]. This is unlikely to affect pregnancy progression and outcomes or cause significant discomfort.

Compensation/Indemnity

If you, as a participant of this research, suffer injury, compensation may, at the discretion of the researcher or sponsor of the research, be paid without litigation. However, compensation is not automatic and you may have to take legal action in order to receive payment.

Payment/Cost

To compensate you for any inconvenience you experience as a result of this study you will be paid **$350** in total for completion of the study. This will be paid in $50 instalments throughout the study. You will receive 2 instalments during your pregnancy, 1 instalment after the birth of your baby, 1 instalment when your baby is 4 months old and an instalment at each yearly visit until your child is 3 years old (7 instalments in total). Any additional tests involved in this study that are outside your routine medical checkups will be conducted at no cost to you. As a special thank you to your baby/child for their involvement, they will receive a small gift at each follow up visit, beginning when they are 4 months of age. We will also pay for a taxi or car-parking fees when you come for additional visits including the 4 month follow-up visit to the hospital.

Study timetable for control subjects

Time	Routine Visit	Questionnaires	Maternal Urine Samples	Maternal Blood Samples — Drug concentrations	Liver and kidney function	Finnegan Scale
Antenatal	Screening and consent form collection will occur on the first antenatal visit					
Up to week 11	X — At any routine visit	X	3 random urine samples	3 blood samples taken on the day of the urine sample	1 blood sample at enrolment	
Week 12	X	X				
Week 16	X	X				
Week 18	X	X				
Week 22		X				
Week 26		X				
Week 28	X	X				
Week 30		X	3 random urine samples	3 blood samples taken on the day of the urine sample		
Week 32	X	X			X	
Week 34	X	X				
Week 36	X	X				
Week 37	X	X				
Week 38	X	X				
Week 39	X	X				
Week 40	X	X				
Postnatal						
Week 1		X	**X**	**X**		X 4-hourly until discharge
Week 2		X		X		X
Week 3		X		X		X
Week 4		X		X		X
4 Months		X	Visit to the hospital to assess Visual Evoked Potential of your baby			
1 Year		X	Visit to your home to assess the development of your child			
2 Years		X	Visit to your home to assess the development of your child			
3 Years		X	Visit to your home to assess the development of your child			

Questionnaires to be completed:
Structured initial interview (first visit only)
Other drug use/co-medication questionnaire (self-report)
From 4 months to 3 years of age: questionnaire to assess your child's development, your health, your household environment and your current family situation.

If at any time you wish to contact the project team, please ring:
Pregnancy and the Neonatal Period
- Ms Justine Whitham (Tel:).
- Dr Olga Lopatko (Tel:).

Follow-up of Your Child
- Dr Nicola Spurrier (Tel:).
- Ms Justine Whitham (Tel:).

This study has been reviewed by the Women's and Children's Hospital Research Ethics Committee. Should you wish to discuss the study with someone not directly involved, in particular in relating to matters concerning policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Research Coordinator at the Women's and Children's Hospital, Ms Brenda Penny (Tel:).

Appendix F. Consent Form for Control Group Participants

Study Title: Buprenorphine and methadone in pregnancy: Effects on the developing infant and child.

1. I . . . . (please print) hereby consent to take part in the research project entitled **"***Buprenorphine and methadone in pregnancy: Effects on the developing infant and child***."** I have read the Information Sheet and understood its contents. I have had the nature and purpose of the research project, so far as it affects me, fully explained to my satisfaction by the research worker. My consent is freely given.

2. I understand that I may not directly derive any clinical benefit from taking part in the research project.

3. I acknowledge that the details of the following procedures, including possible risks and or side effects, discomforts and inconveniences have been explained to me
   * Collection of blood and urine samples from myself
   * Visual Evoked Potential assessment of my infant at 4 months of age
   * Developmental assessments of my infant/child at 12, 24 and 36 months of age

4. I understand that while information gained during the research project may be published, I will not be identified and my personal results will remain confidential.

5. I understand that I may withdraw from the research project at any stage, without giving a reason, and that this will not affect my medical care, now or in the future.

6. I understand the statement concerning payment, which is contained in the Information Sheet.

7. I have had the opportunity to discuss taking part in the research project with a family member or friend.

8. I am aware that I should retain a copy of this Consent Form, when completed, and the information sheet.

Signed . . . .   Date . . . .

Witness Signature . . . .   Date . . . .

      Name . . . .

I . . . .   certify that I have explained the nature and procedures of the research

project to . . . .   and consider that he/she understands what is involved.

Signed . . . .   Date . . . .

Status in Project   . . . .

Appendix G. Initial Study Assessment

Subject initials: ☐☐☐   **Subject code:** ☐☐☐☐☐

Date today: ☐☐■☐■☐   *CON*trol/*BUP*renorphine/*MET*hadone: ☐☐☐

Gestational age (weeks): ☐☐   **Expected date of delivery:** ☐☐■☐■☐

Section A: Demographics & Medical History

A1 **Date of Birth:** ☐☐■☐■☐☐

A2 **Ethnicity:** Caucasian….. ☐   **A3 Post code:** ☐☐☐☐

Asian………. ☐

Aboriginal….. ☐

Other……….. ☐   If other, please specify: _____

A4 **Education:** Highest level of education completed by the subject?

Year 10………. ☐   TAFE/ Apprenticeship….. ☐

Year 11………. ☐   University degree………. ☐

Year 12………. ☐   Other…………………. ☐

If other, please specify: _____

A5 **Employment History:** <u>Usual</u> occupation of subject over the last three years?

Professional….. ☐   Skilled/Trade…. ☐   Unskilled………. ☐

Student………. ☐   Home duties….. ☐   Unemployed…… ☐

Other………… ☐   If other, please specify: _____

A6 **Marital/Parental Status:**

Partner ☐ yes ☐ no   Living with partner   yes ☐ no ☐

Married ☐ yes ☐ no   Divorced/Separated   yes ☐ no ☐

No. of children ☐   Children's ages   1 ☐ 2 ☐ 3 ☐ 4 ☐

No. of terminations ☐   No. of miscarriages ☐

Other ☐   If other, please specify: _____

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A7 **Medical History:** List all significant medical conditions recorded at, and since, start of current maintenance programme (use other side of page if necessary)

	Condition	Started (at least year)	Outcome (resolved/ongoing)
A7.1	_____	☐☐■☐☐■☐☐	_____
A7.2	_____	☐☐■☐☐■☐☐	_____
A7.3	_____	☐☐■☐☐■☐☐	_____

Section B: Drug Use History

B1 Heroin

B1.1 Age of first heroin use............................………. ☐☐ years

B1.2 Age of first daily heroin use................................. ☐☐ years

B1.3 Length of consistent heroin use prior to entry………. ☐☐ months
i.e. no interruptions greater than 1 week

B1.4 Average monthly heroin use prior to entry..............days per month ☐☐

B1.5 Average daily heroin use prior to entry................... ☐☐ times per day

B1.6 Average daily heroin cost prior to entry............ ☐☐☐ $ per day used (= $/time x times/day)

B2 Other Drugs

	Recreational Use Only	Ever Used		If YES, what was average use at start of current maintenance programme			
		YES	NO	Days used in month prior	Route of administration (*see below)	Frequency per day used	Average cost per day used
B2.1	Alcohol.................	☐	☐	☐☐		☐☐	☐☐
B2.2	Tobacco...............	☐	☐	☐☐		☐☐	☐☐
B2.3	Street methadone not prescribed for you	☐	☐	☐☐	☐	☐☐	☐☐
B2.4	Other opiates...... morphine, pethidine, codeine, mersyndol	☐	☐	☐☐	☐	☐☐	☐☐
B2.5	Amphetamines..... speed	☐	☐	☐☐	☐	☐☐	☐☐

B2.6	Cocaine.............. including crack	☐	☐	☐☐	☐	☐☐	☐☐
B2.7	Ecstasy...............	☐	☐	☐☐	☐	☐☐	☐☐
B2.8	Hallucinogens...... LSD, mushrooms, acid	☐	☐	☐☐	☐	☐☐	☐☐
B2.9	Marijuana............ cannabis, dope	☐	☐	☐☐	☐	☐☐	☐☐
B2.10	Benzodiazepines. Rohypnol, Valium, Serepax, Mogadon	☐	☐	☐☐	☐	☐☐	☐☐
B2.11	Inhalants. Glue, nitrous, petrol	☐	☐	☐☐	☐	☐☐	☐☐

* **i** = inject; **o** = oral; **s** = smoke; **n** = nasal

Section C: Drug Treatment History

C1 Current Treatment for Opioid Dependence

C1.1   Currently in maintenance treatme☐   yes☐   no

C1.2   Which treatment? _____   Number of episodes (this treatment☐

Date started

C1.3   Length of current maintenance treatment ☐☐ months   ☐☐■☐☐■☐☐

C1.4   Current maintenance treatment dose ☐☐ mg

C1.5   Current stream   A ☐   B ☐   C ☐

C2 Previous Treatment for Opioid Dependence

C2.1   No previous opioid treatment   ....   If no previous opioid treatments, go to Question C3

		YES	NO	If YES: no. of times + comments
C2.2	Previous methadone maintenance	☐	☐	☐ _____
C2.3	Previous LAAM maintenance	☐	☐	☐ _____
C2.4	Previous SROM maintenance	☐	☐	☐ _____
C2.5	Previous buprenorphine maintenance	☐	☐	☐ _____
C2.6	Previous naltrexone maintenance	☐	☐	☐ _____
C2.7	Detox - clinic	☐	☐	☐ _____
C2.8	Detox - home (medically supervised)	☐	☐	☐ _____

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C2.9	Drug free counselling	....	☐	☐	☐	_____
C2.10	Therapeutic community	....	☐	☐	☐	_____
C2.11	Narcotics Anonymous	....	☐	☐	☐	_____
C2.12	Other: _____	....	☐	☐	☐	_____

C3 Other Drug Treatments

C3.1   Have you tried any treatment for other drug use?   YES ☐   NO ☐

If YES, please give details:

	Drug	Treatment	No. of times
C3.3	_____	_____	☐
C3.3	_____	_____	☐
C3.4	_____	_____	☐

Section D: Criminal & Legal History

D1 Criminal Activity

Have you ever been involved in any of the following?

		YES	NO	If YES age at first occurrence	Most recent occurrence Month / Year
D1.1	Dealing: Heroin	☐	☐	☐☐	☐☐■☐☐
D1.2	Dealing: Other drugs.............................	☐	☐	☐☐	☐☐■☐☐
D1.3	Break & Enter: Domestic (house, shed)	☐	☐	☐☐	☐☐■☐☐
D1.4	Break & Enter: Domestic (shop, business).	☐	☐	☐☐	☐☐■☐☐
D1.5	Assault: Snatch & Grab	☐	☐	☐☐	☐☐■☐☐
D1.6	Assault: Injurious	☐	☐	☐☐	☐☐■☐☐
D1.7	Fraud	☐	☐	☐☐	☐☐■☐☐
D1.8	Shoplifting	☐	☐	☐☐	☐☐■☐☐
D1.9	Prostitution	☐	☐	☐☐	☐☐■☐☐
D1.10	Armed Robbery	☐	☐	☐☐	☐☐■☐☐
D1.11	Stolen car	☐	☐	☐☐	☐☐■☐☐

D2 Legal Pressures

Have any of the following ever happened to you?

		YES	NO	If YES age at first occurrence	Most recent occurrence Month / Year
D2.1	Police: Cautioned/Questioned	☐	☐	☐☐	☐☐■☐☐
D2.2	Police: Lock-up	☐	☐	☐☐	☐☐■☐☐
D2.3	Police: Arrested	☐	☐	☐☐	☐☐■☐☐
D2.4	Imprisonment	☐	☐	☐☐	☐☐■☐☐
D2.5	Community Service	☐	☐	☐☐	☐☐■☐☐
D2.6	Court Appearance	☐	☐	☐☐	☐☐■☐☐

D2.7 Were legal pressures a reason for joining program? YES ☐ NO ☐

Investigator Signature: ………………………… Date: …………………………

Appendix H. Modified Finnegan Scale

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┌─────────────────────────────────────────────────┐
│                     NOTE:                         │
│   This appendix is included on page 78 (Volume 2) of the print │
│   copy of the thesis held in the University of Adelaide Library. │
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From NSW Methadone Maintenance Treatment Clinical Practice Guidelines. Used with permission.

INFANT DATA COLLECTION INSTRUCTIONS

- Administer the Modified Finnegan Withdrawal Scale at least every four hours from delivery. Scoring should encompass all signs since the last feed and be documented before the feed begins, preferably when the infant begins to wake. Scoring should be completed at the end of feed time.
- As this chart is designed for term babies who are fed fourth hourly, adjustments must be made for breast feeders, demand fed infants and preterm infants.
- Record dose of any infant medication being taken at each Finnegan scoring session.
- Encourage parental involvement in noticing signs but parents are not to score their infants.
- Each time baby changes wards start a new Modified Finnegan Withdrawal Scale sheet ensuring the ward name is written on the top of the sheet.

EXTRA SCORING INFORMATION

High-pitched cry	Score 2 if a cry is high pitched at its peak. Score 3 if a cry is high pitched throughout.
Sleep	If infant wakes and settles after a nappy change or burp this is in the range of normal behaviour. If infant is demand breastfed see feeding. Total the time infant is awake and requiring attention.
Tremors	This is a scale of increasing severity and baby should only receive one score from each of the two categories. Undisturbed means when baby is asleep or at rest in a cot.
Increased muscle tone	Score if muscle tone is greater than the upper limit of normal.
Excoriation	Score when it presents, increases in severity or appears in another area.
Fever	Infants should be swaddled in a cotton sheet then covered with the same number of blankets as any other baby.
Yawning and sneezing	Score if more than 3-4 times in 30 minutes.
Nasal flaring/respiratory rate	Score if present without other evidence of respiratory disease.
Excessive sucking	Score after feeding, excessive if more than a hungry normal baby.
Poor feeding	Accurate assessment of supply and attachment must be made. Look for signs of disorganisation that lead to slow feeding or taking inadequate amounts. Compliment with formula until supply is established if baby does not settle on breast milk alone.
Regurgitation	Score if occurs more frequently than usual in newborn.

Appendix I. Treatment and weaning protocol for Neonatal Abstinence Syndrome

Treatment Instructions:

Modified Finnegan Score	Morphine Therapy
0-7	0mg
8-10	0.5mg/kg/day 4 hourly
11-13	0.7mg/kg/day 4 hourly
14+	0.9mg/kg/day 4 hourly

Weaning Instructions:

Once abstinence has been controlled (three consecutive scores less than 8) using this dosage regime, the following should be implemented: Please note that all doses for entire period of withdrawal management are calculated on birth weight and not current weight.

- Maintain control for 72 hours.
- Initiate the detoxification process by decreasing the total daily dose by 10% every 72 hours.
- When dosage levels reach 0.2 mg/kg/day – maintain this dose for 72 hours. At this dose, consideration can be given to home management (see below).
- Change from 4 hourly to 6 hourly dosage regime (same dose) for 72 hours prior to ceasing all medication.
- When oral morphine treatment is discontinued, the NASS should continue for a further 72 hours.

Supportive therapy (using a pacifier, swaddling, close wrapping, small frequent feeds, providing close skin contact) is an important adjunct to medical therapy.

If an infant is vomiting in association with morphine dosing, ensure that the infant is not being overfed and that the infant is being appropriately postured during and after feeding. Give the morphine before the feed. If baby has a large vomit after being given morphine:

1. if vomits within 10 minutes of dose, re-dose
2. if vomits after 10 minutes of dose, give ½ dose
3. if baby vomits after feed, do not give further morphine (always err on side of caution).

Child Health and Development Study

Name of Parent: _____

Name of Child: _____

Date of Interview: _____

Name of Interviewer: _____

this information will be removed from
the front of this booklet

Instructions

This booklet asks about your child's health. It also asks questions about yourself and your family. Your individual answers will not be shared with anyone.

Some questions require you to tick boxes, whilst others will ask you to circle a response. Please answer each section of the questionnaire after reading the instructions carefully.   It is important that you follow the instructions, otherwise we can't use the information you give us. If you are unsure which answer to choose, please give the best answer you can and make a comment in the margin.

Certain questions may look alike, but each one is different. Some questions may ask about problems you or your family may not have. That's great, but it is important for us to know. Please answer each question.

The pages in this booklet are double-sided. Please make sure you answer questions on both sides of the paper.

There are no right or wrong answers; we are interested in your views and opinions. All of the information you provide will be completely confidential so please be as honest and accurate as possible

GROWTH AND VEP RECORD FORM
Section 1. Your Child

YOUR CHILD'S MEASUREMENTS

Height/ Length (cm)	
Weight (kg)	
Head Circumference (cm)	

VISUAL EVOKED POTENTIAL SCORES

	VEP Latency	
File Numbers		
Trigger Used	Yes ☐　　　　No ☐	
Line Filter	In　☐　　Out　☐	
	Checksize 8 Run 1: _____ Run 2: _____ Run 3: _____ Av. (ms^{-1}): 　_____	**Checksize 12** Run 1: _____ Run 2: _____ Run 3: _____ Av. (ms^{-1}): 　_____
No. of runs		
Comments		

SLEEP AND HEALTH RECORD FORM

Your Child's Health

On average…..

How many hours does your child spend in sleep during the <u>night</u> (between 7pm and 7am)? _____

How many hours does your child spend in sleep during the <u>day</u> (between 7am and 7pm)? _____

How many times does your child wake up during the night? _____

How many hours does your child spend awake during the night (between 10pm and 6am)? _____

How long does it take to put your child to sleep in the evening? _____

When does your child usually fall asleep for the night? _____

Do you consider your child's sleep a problem?

No ☐
Yes ☐
Unsure ☐

Has your child had any medical problems in the last 4 months?

No ☐
Yes ☐
(please describe) _____

_____

Has your child had any seizures/fits/convulsions in the last 4 months?

No ☐
Yes ☐ **(please go to Question 10)**

Did any of these seizures/fits/convulsions occur when your child had a temperature?

No ☐
Yes ☐

<u>BREASTFEEDING RECORD FORM</u>

Feeding Your Child

What method of feeding are you using at the moment?

Fully Breastfeeding
(This means giving your baby breast milk only).

Partially Breastfeeding
(This means giving your baby breast milk <u>and</u> formula)

Fully Bottle-feeding
(This means giving your baby formula)

If you have stopped breastfeeding, how old was your baby when you stopped breastfeeding? _____

Have you started giving your baby solids?

No ☐
Yes ☐

SHORT TEMPERAMENT SCALE FOR INFANTS

Your Child's Behaviour

This page in the questionnaire booklet contained the <u>Short Temperament Scale for Infants</u>. For copyright reasons it could not be reproduced here.

Section 2. Your Health

This page in the questionnaire booklet contained the <u>General Health Questionnaire</u>. For copyright reasons it could not be reproduced here.

MATERNAL POSTNATAL ATTACHMENT SCALE
Feelings About Your Baby

The following questions ask about feelings you may have towards your baby
Please place a tick in the box next to the answer that comes closest to how you feel about your baby.

1.   When I am caring for the baby, I get feelings of annoyance or irritation

      very frequently   ☐
      frequently   ☐
      occasionally   ☐
      very rarely   ☐
      never   ☐

2.   When I am caring for the baby I get feelings that the child is deliberately being difficult or trying to upset me

      very frequently   ☐
      frequently   ☐
      occasionally   ☐
      very rarely   ☐
      never   ☐

3.   Over the last two weeks I would describe my feelings for the baby as

      dislike   ☐
      no strong feelings towards the baby ☐
      slight affection   ☐
      moderate affection   ☐
      intense affection   ☐

4.   Regarding my overall level of interaction with the baby

      I feel very guilty that I am not more involved   ☐
      I feel moderately guilty that I am not more involved ☐
      I feel slightly guilty that I am not more involved   ☐
      I don't have any guilty feelings regarding this   ☐

5.   When I interact with the baby I feel

      very incompetent and lacking in confidence   ☐
      moderately incompetent and lacking in confidence ☐
      moderately competent and confident   ☐
      very competent and confident   ☐

6.   When I am with the baby I feel tense and anxious

      very frequently   ☐
      frequently   ☐
      occasionally   ☐
      almost never   ☐

7. When I am with the baby and other people are present I feel proud of the baby

very frequently ☐
frequently ☐
occasionally ☐
almost never ☐

8. I try to spend as much time as I possibly can <u>playing</u> with the baby

this is true ☐
this is untrue ☐

9. When I have to leave the baby

I usually feel rather sad (or it's difficult to leave) ☐
I often feel rather sad (or it's difficult to leave) ☐
I have mixed feelings of both sadness and relief ☐
I often feel rather relieved (and it's easy to leave) ☐
I usually feel rather relieved (and it's easy to leave) ☐

10. When I am with the baby

I always get a lot of enjoyment/satisfaction ☐
I frequently get a lot of enjoyment/satisfaction ☐
I occasionally get a lot of enjoyment/satisfaction ☐
I very rarely get a lot of enjoyment/satisfaction ☐

11. When I am not with the baby I find myself thinking about the baby

almost all the time ☐
very frequently ☐
frequently ☐
occasionally ☐
not at all ☐

12. When I am with the baby

I usually try to prolong the time I spend with him/her ☐
I usually try to shorten the time I spend with him/her ☐

13. When I have been away from the baby for awhile and I am about to be with him/her again, I usually feel

intense pleasure at the idea ☐
moderate pleasure at the idea ☐
mild pleasure at the idea ☐
no feelings at all about the idea ☐
negative feelings about the idea ☐

14. I now think of the baby as

very much my own baby ☐
a bit like my own baby ☐
not yet really my own baby ☐

15.   Regarding the things that I/we have had to give up because of this baby

I find that I resent it quite a lot ☐
I find that I resent it a moderate amount ☐
I find that I resent it a bit ☐
I don't resent it at all ☐

16.   Over the past six months I have felt that I do not have enough time for myself or to pursue my own interests

almost all the time ☐
very frequently ☐
frequently ☐
occasionally ☐
not at all ☐

17.   Taking care of this baby is a heavy burden of responsibility. I believe this is

very much so ☐
somewhat so ☐
slightly so ☐
not at all ☐

18.   I trust my own judgement in deciding what the baby needs

almost never ☐
occasionally ☐
most of the time ☐
almost all the time ☐

19.   Usually when I am with the baby

I am very impatient ☐
I am a bit impatient ☐
I am moderately patient ☐
I am extremely patient ☐

Source: Condon, J. T., & Corkindale, C. J. (1998). The assessment of parent-to-infant attachment: Development of a self-report questionnaire instrument. *Journal of Reproductive and Infant Psychology, 16*(1), 57-77.

EDINBURGH POSTNATAL DEPRESSION SCALE
Your Emotional Health

NOTE:
This scale is included on pages 91-92 (Volume 2) of the print copy of the thesis held in the University of Adelaide Library.

Source: Cox, J.L., Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786.

Social Interaction

This page in the questionnaire booklet contained the <u>Interview Schedule for Social Interaction-Short Form</u>. For copyright reasons it could not be reproduced here

Substance Use Checklist

All questions in this questionnaire are about what has happened to you since your last visit. Any information you give here is completely confidential. Please answer all questions honestly and accurately.

Buprenorphine/methadone only	Dose:	
Time of dose today		
Time of dose yesterday		
Time of dose day before yesterday		

Tobacco Yes/No	In the last month	Since your last study visit
How many cigarettes per day?		
How many mg?		

Heroin Yes/No	In the last month	Since your last study visit
Number of days used?		
Number of times used on those days?		
Cost per day on days used?		

Other opioids Yes/No	In the last month	Since your last study visit
Which substance (kapanol, morphine, pethidine, oxycodone, codeine etc)?		
How did you take this substance?		
Number of days used?		
Number of times used on those days?		

Alcohol Yes/No	In the last month	Since your last study visit
Number of days consumed?		
Number of drinks per day on days consumed?		

Marijuana Yes/No	In the last month	Since your last study visit
Number of days used ?		
How many cones/joints per day on days used?		

Amphetamines Yes/No	In the last month	Since your last study visit
Which substance (cocaine, ecstasy, methamphetamine etc)?		
How did you take this substance?		
Number of days used?		
Number of times used on those days?		

Inhalants Yes/No	In the last month	Since your last study visit
Which substance (petrol, glue, aerosol etc)?		
Number of days used?		
Number of times used on those days?		

Hallucinogens Yes/No	In the last month	Since your last study visit
Which substance (LSD, acid, mushrooms etc)?		95
Number of days used?		
Number of times used on those days?		
Benzodiazepines Yes/No	In the last month	Since your last study visit
Which substance (diazepam, temazepam, oxazepam, Rohypnol etc)?		
How did you take this substance?		
Number of days used?		
Number of times used on those days?		
Other medication Yes/No	In the last month	Since your last study visit
Which substance?		
How did you take this substance?		
Number of days used?		
Number of times used on those days?		

Background Information

1. What is the sex of the child in this study?

   Male ☐
   Female ☐

2. What is the age of the child in this study?

   _____ years _____ months

3. What is your age?

   _____ years

4. What are the ages of <u>all other</u> dependent children (18 years or younger) in your home?

   ____ ____ ____ ____ ____

5. Which of the following best describes your relationship to the child in this study?

   Natural mother ☐
   Natural father ☐
   Stepmother ☐
   Stepfather ☐
   Other (please describe): _____

6. Which of the following best describes the parents living in the child's household?
   Two natural parents ☐
   Mother and stepfather/defacto ☐
   Father and stepmother/defacto ☐
   Mother alone ☐
   Father alone ☐
   Other (please describe):
   _____

7. Since your baby was born, how many times have you changed where you and your baby live?

   _____ times

8. Since your baby was born have there been any changes in your living arrangements (eg separation from partner) for you and your baby?

   No ☐
   Yes ☐
   Please describe: _____

9. What is the usual occupation of the mother (or parental mother figure) in the child's household?

_____

(Please describe)

10. Is the <u>mother</u> in the child's household currently in paid employment?

No ☐
Yes ☐

If yes, on what basis?
Casual ☐
Contract ☐
Permanent ☐
Hours per week _____

11. What is the mother's (or parental mother figure's) highest completed level of schooling?

Primary school ☐
Some years of high school ☐
Year 12, Matric or equivalent ☐
Technical, trade or TAFE certificate ☐
Tertiary qualifications ☐

12. What is the usual occupation of the father (or parental father figure) in the child's household?

_____

(Please describe)

13. Is the <u>father</u> in the child's household currently in paid employment?

No ☐
Yes ☐

14. What is the father's (or parental father figure's) highest <u>completed</u> level of schooling?

Primary school ☐
Some years of high school ☐
Year 12, Matric or equivalent ☐
Technical, trade or TAFE certificate ☐
Tertiary qualifications ☐

15. Before tax, what is your gross <u>household</u> income per year from all sources (eg wages, family payment, child maintenance etc)

$0-$10,400 ☐
$10,401-$31,200 ☐
$31,201-$52,000 ☐
more than $52,000 ☐

16. Does your family receive any pension or benefit?

No ☐
Yes ☐
Please describe: _____
_____

17. How would you describe your home at the moment?

Housing trust – renting ☐
Housing trust – purchasing ☐
Renting house or unit ☐
Being purchased ☐
Fully owned ☐
Living with your parents or your partner's parents ☐
Occupying house or unit rent free ☐
Caravan or Caravan Park ☐
Other (please describe): _____

Thank you very much for your help with the Childhood Health and Development Study

CAREGIVER QUESTIONNAIRE (12 & 24 MONTHS)

Child Health and Development Study

Name of Parent: _____

Name of Child: _____

Date of Interview: _____

Name of Interviewer: _____

this information will be removed from
the front of this booklet

Instructions

1. This booklet asks about your child's health. It also asks questions about yourself and your family. Your individual answers will not be shared with anyone.

2. Some of the questions are the same or similar to the ones you answered when your child was 4 months old. This is because we would like to measure any changes over time.

3. Some questions require you to tick boxes, whilst others will ask you to circle a response. Please answer each section of the questionnaire after reading the instructions carefully.   It is important that you follow the instructions, otherwise we can't use the information you give us. If you are unsure which answer to choose, please give the best answer you can and make a comment in the margin.

4. Certain questions may look alike, but each one is different. Some questions may ask about problems you or your family may not have. That's great, but it is important for us to know. Please answer each question, even if your answer is a 'no'.

5. The pages in this booklet are double-sided. Please make sure you answer questions on both sides of the paper.

6. There are no right or wrong answers; we are interested in your views and opinions. All of the information you provide will be completely confidential so please be as honest and accurate as possible.

Section 1. Your Child

YOUR CHILD'S MEASUREMENTS

Height/ Length (cm)	
Weight (kg)	
Head Circumference (cm)	

Your Child's Health

On average…..

1. How many hours does your child spend in sleep during the **<u>night</u>** (between 7pm and 7am)? _____

2. How many hours does your child spend in sleep during the **<u>day</u>** (between 7am and 7pm)? _____

3. How many times does your child wake up during the night? _____

4. How many hours does your child spend awake during the night (between 10pm and 6am)? _____

5. How long does it take to put your child to sleep in the evening? _____

6. What time does your child usually fall asleep for the night? _____

7. Do you consider your child's sleep a problem?

   No   ☐
   Yes   ☐
   Unsure   ☐

8. Has your child had any medical problems in the last 9 months (since the 4 month visit)?

   No   ☐
   Yes   ☐
   (please describe) _____
   _____
   _____
   _____
   _____
   _____

9. Has your child had any seizures/fits/convulsions in the last 9 months (since the 4 month visit)?

   No   ☐
   Yes   ☐ (please go to Question 10)

10. Did any of these seizures/fits/convulsions occur when your child had a temperature (ie a febrile convulsion)?

No ☐
Yes ☐

11. Did any of these seizures/fits/convulsions occur when your child <u>did not</u> have a temperature (ie a febrile convulsion)?

No ☐
Yes ☐

Feeding Your Child

1. Are you still breastfeeding your baby/toddler?

No ☐
Yes ☐

2. If you have stopped breastfeeding, how old was your baby/toddler when you stopped breastfeeding? _____

3. How old was your child when you first introduced solid foods?

4. Which solid foods have you introduced to your child's diet? (please tick those that apply)

Red meat ☐
Chicken ☐
Fish ☐
Cheese ☐
Vegetables ☐
Rice cereal ☐
Fruits ☐
Yoghurt ☐
Egg ☐
Bread/crackers/rice ☐

Your Child's Behaviour

This page in the questionnaire booklet contained the <u>Short Temperament Scale for Toddlers</u>. For copyright reasons it could not be reproduced here.

Your Child's Environment

This page in the questionnaire booklet contained the <u>Infant HOME Inventory</u>. For copyright reasons it could not be reproduced here.

Section 2. Your Health

We would like to know if <u>you</u> have had any medical complaints, and how <u>your</u> health has been in general, <u>over the past few weeks</u>. Please answer ALL of the questions on the following pages simply by circling the answer which you think most correctly applies to you. Remember we want to know about <u>present</u> and <u>recent</u> complaints, not those that you may have had in the past.

This page in the questionnaire booklet contained the <u>General Health Questionnaire</u>. For copyright reasons it could not be reproduced here.

Parenting Stress

This page in the questionnaire booklet contained the <u>Parent Domain</u> of the <u>Parenting Stress Index</u>. For copyright reasons it could not be reproduced here.

Social Interaction

This page in the questionnaire booklet contained the <u>Interview Schedule for Social Interaction-Short Form</u>. For copyright reasons it could not be reproduced here

Substance Use Checklist

All questions in this questionnaire are about what has happened to you since your last visit. Any information you give here is completely confidential. Please answer all questions honestly and accurately.

Buprenorphine/methadone only	Dose:
Time of dose today	
Time of dose yesterday	
Time of dose day before yesterday	

Tobacco Yes/No	In the last month	Since your last study visit
How many cigarettes per day?		
How many mg?		

Heroin Yes/No	In the last month	Since your last study visit
Number of days used?		
Number of times used on those days?		
Cost per day on days used?		

Other opioids Yes/No	In the last month	Since your last study visit
Which substance (kapanol, morphine, pethidine, oxycodone, codeine etc)?		
How did you take this substance?		
Number of days used?		
Number of times used on those days?		

Alcohol Yes/No	In the last month	Since your last study visit
Number of days consumed?		
Number of drinks per day on days consumed?		

Marijuana Yes/No	In the last month	Since your last study visit
Number of days used?		
How many cones/joints per day on days used?		

Amphetamines Yes/No	In the last month	Since your last study visit
Which substance (cocaine, ecstasy, methamphetamine etc)?		
How did you take this substance?		
Number of days used?		
Number of times used on those days?		

Inhalants Yes/No	In the last month	Since your last study visit
Which substance (petrol, glue, aerosol etc)?		
Number of days used?		
Number of times used on those days?		

Hallucinogens Yes/No	In the last month	Since your last study visit
Which substance (LSD, acid, mushrooms etc)?		
Number of days used?		
Number of times used on those days?		
Benzodiazepines Yes/No	In the last month	Since your last study visit
Which substance (diazepam, temazepam, oxazepam, Rohypnol etc)?		
How did you take this substance?		
Number of days used?		
Number of times used on those days?		
Other medication Yes/No	In the last month	Since your last study visit
Which substance?		
How did you take this substance?		
Number of days used?		
Number of times used on those days?		

Background Information

1.   What is the sex of the child in this study?

       Male   ☐
       Female   ☐

2.   What is the age of the child in this study?

       _____ years

3.   What is your age?

       _____ years

4.   What are the ages of <u>all other</u> dependent children (18 years or younger) in your home?

       ____ ____ ____ ____ ____

5.   Which of the following best describes your relationship to the child in this study?

       Natural mother   ☐
       Natural father   ☐
       Stepmother   ☐
       Stepfather   ☐
       Other (please describe): _____

6.   Which of the following best describes the parents living in the child's household?
       Two natural parents   ☐
       Mother and stepfather/defacto   ☐
       Father and stepmother/defacto   ☐
       Mother alone   ☐
       Father alone   ☐
       Other (please describe):

       _____

7. Since we last saw you (when your child was 4 months old), how many times have you changed where you and your child live?

_____ times

8. Since we last saw you (when your child was 4 months old) have there been any changes in your living arrangements (eg separation from partner) for you and your child?

No ☐
Yes ☐
Please describe: _____

_____

9. What is the usual occupation of the mother (or parental mother figure) in the child's household?

_____
(Please describe)

10. Is the <u>mother</u> in the child's household currently in paid employment?

No ☐
Yes ☐

If yes, on what basis?
Casual ☐
Contract ☐
Permanent ☐
Hours per week _____

11. What is the mother's (or parental mother figure's) highest completed level of schooling?

Primary school ☐
Some years of high school ☐
Year 12, Matric or equivalent ☐
Technical, trade or TAFE certificate ☐
Tertiary qualifications ☐

12. What is the usual occupation of the father (or parental father figure) in the child's household (if applicable)?

_____
(Please describe)

13. Is the <u>father</u> in the child's household currently in paid employment?

No ☐
Yes ☐
N/A ☐

14. What is the father's (or parental father figure's) highest <u>completed</u> level of schooling?

Primary school ☐
Some years of high school ☐
Year 12, Matric or equivalent ☐
Technical, trade or TAFE certificate ☐
Tertiary qualifications ☐
N/A ☐

15. Before tax, what is your gross <u>household</u> income per year from all sources (eg wages, family payment, child maintenance etc)

$0-$10,400 ☐
$10,401-$31,200 ☐
$31,201-$52,000 ☐
more than $52,000 ☐

16. Does your family receive any pension or benefit?

No ☐
Yes ☐
Please describe: _____

_____

17. How would you describe your home at the moment?

Housing trust – renting ☐
Housing trust – purchasing ☐
Renting house or unit ☐
Own house/unit - purchasing ☐
Own house/unit - fully owned ☐
Living with your parents or your partner's parents ☐
Occupying house or unit rent free ☐
Caravan or Caravan Park ☐
Other (please describe): _____

Thank you very much for your help with the Childhood Health and Development Study

Appendix K. Uncontactable Letter

Government of South Australia

Children, Youth and Women's
Health Service

Women's
& Children's
Hospital

Date

Dear <Parent's name>,

It is now time for the 2 year follow-up assessment in the Child Health and Development Study in which you and <Child's name> are participating.

Unfortunately, I have been unable to contact you by telephone. I would be very pleased if you would agree to continue with this important study.

During this visit I will visit you in your home or somewhere convenient for you and weigh and measure <Child's name>. I will also assess <Child's name> on the Bayley Scales of Infant Development and ask you to complete a questionnaire. The visit should take between 60 to 90 minutes.

To thank you for your time we will provide a payment of $50. As a special thank you to <Child's name> for his/her involvement, he/she will receive a small gift.

Please text or telephone Justine Whitham at the Research and Evaluation Unit, Women's and Children's Hospital on   or leave a message on   to tell us the best way to contact you.

Yours sincerely

Justine Whitham
Research Assistant
Child Health and Development Study
Research and Evaluation Unit
Women's and Children's Hospital

Appendix L. Example Report

Developmental Assessment Report – 2 years

Child Health and Development Study

Personal Information

Name: Child   Date of Assessment: 31/01/08

Date of Birth: 14/12/06   Age at Assessment: 13 months, 17 days
                                                           Corrected age: 12 months, 21 days

Parents: Mother and Father   Place of Testing: Child's home

Weight: 11.85kg (just above 90th percentile)
Length: 79.0cm (75th percentile)
Head Circumference: 48.0cm (50-98th percentile)

Assessed by: Justine Whitham

This assessment is part of the Child Health and Development Study. It is important to note that the results of this test represent a general indication of this child's presentation on the testing day, rather than a clinical assessment.

Assessment Instruments

Bayley Scales of Infant Development
The Bayley Scales of Infant Development is a standardised test that measures the development of children's thinking and movement abilities, as well as their behaviour during the test period. The Scales are used for children aged between 1 month and 3 years, 6 months. Aspects of development such as memory, simple problem solving, language abilities, body control, coordination, and fine motor movement are tested via observations and a series of simple tasks for children. A child's performance on these items, together with parents' observations, yield estimates of the child's current functioning, compared to other children of their age. The Scales have been administered to many thousands of children to provide this comparative information. Information about a child's pattern of abilities and any areas of strength and weakness can be helpful in planning activities and/or any specific interventions necessary. It is important to note that a child's performance on the Bayley Scales does not necessarily predict how they will perform at school, or in later testing of intellectual functioning.

Observations during Testing
Child presented as a happy and placid child who was easy to engage and did not show any unusual fear of the examiner. He demonstrated keen interest in the test items and attempted the majority of them with initiative and enthusiasm. Child was generally cooperative and showed good attention and concentration throughout the assessment, despite obvious tiredness. He was persistent when attempting the more complex activities and did not easily become frustrated. Child made many attempts to interact socially with his parents and the examiner, smiling and giggling throughout the assessment and continuing a game of 'peek-a-boo' with his father. Child's parents reported that his behaviour on the day of testing was somewhat typical of Child and that he was tired and had an ear infection at the time of

assessment. They reported that his performance on the activities was a good indicator of his usual abilities.

Results
Summary of Scores and percentiles

Scales	Percentile	Range
Mental Scale Total Score	25-37	Within Normal Limits
Motor Scale Total Score	16-25	Within Normal Limits
Behaviour Scale Total Score	60	Within Normal Limits

Mental Scale Total Score: This score reflects Child's performance on tasks that require thinking, problem solving and memory. Child's score was "within normal limits" for children of his corrected age group and indicates that he is performing at a level that is equal to, or better than, 25-37% of children his age.

Motor Scale Total Score: This score reflects Child's performance on tasks that require coordination, motor control and balance. Child's score was "within normal limits" for children of his corrected age group and indicates that he is performing at a level that is equal to, or better than, 16-25% of his peers.

Behaviour Scale Total Score: This score indicates how well Child adapted to and engaged with the test materials, his attention, initiative and temperament throughout the testing session and the appropriateness of his motor quality. Child's score was "within normal limits" expected for children of his age, indicating that Child is functioning at a level that is equal to or better than, 60 percent of children the same age.

Summary
Child presented as a happy and engaging child who scored 'Within Normal Limits' on all three scales of the Bayley Scales of Infant Development. The results of this assessment indicate that Child is performing at an overall level that is appropriate for his age group.

I would be happy to discuss the results of this assessment. I can be contacted by telephone on   or   (leave a message if unavailable) and by email: .

Justine Whitham
Research Assistant
Child Health and Development Study
Women's and Children's Hospital

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

Standard linear regression examining the effect of methadone exposure on birth weight (*N*=86)

Variable	*B*±*SE B* (grams)	β	R^2	F
Buprenorphine	-156.33±93.82	-.14	0.56	34.15***
Methadone	-344.41±100.31	-.29**		
Gestational age (weeks)[a]	186.17±21.05	.66***		

Note. Reference group is Control. *p<.05, **p<.01, ***p<.001

[a] *B*±*SE B* are reported in terms of the original distribution, however all other values were calculated using the transformed (power 4) data.

Standard linear regression examining the effect of methadone exposure on birth length (*N*=87)

Variable	*B*±*SE B* (cm)	β	R^2	F
Buprenorphine	-1.27±0.53	-.20*	0.56	34.44***
Methadone	-2.21±0.57	-.31***		
Gestational age (weeks)[a]	1.04±0.12	.64***		

Note. Reference group is Control. *p<.05, **p<.01, ***p<.001

[a] *B*±*SE B* are reported in terms of the original distribution, however all other values were calculated using the transformed (power 4) data.

Standard linear regression examining the effect of methadone exposure on birth head circumference (*N*=86)

Variable	*B*±*SE B* (cm)	β	*R*²	*F*
Buprenorphine	-0.20±0.36	-.06	0.31	12.25***
Methadone	-0.94±0.39	-.25*		
Gestational age (weeks)[a]	0.43±0.08	.47***		

Note. Reference group is Control. *p<.05, **p<.01, ***p<.001

[a] *B*±*SE B* are reported in terms of the original distribution, however all other values were calculated using the transformed (power 4) data.

Appendix N. Publications arising from this work

Peer-reviewed Publications

Whitham, J.N., Spurrier, N.J., Sawyer, M.S., Baghurst, P.A., Taplin, J.E., White, J.M. & Gordon, A.L. (2010). The effects of prenatal exposure to buprenorphine or methadone on infant visual evoked potentials. *Neurotoxicology and Teratology, 32*(2), 280-288.

Conference Presentations

Whitham, J.N., Spurrier, N.J., Sawyer, M.S., Baghurst, P.A., & Taplin, J.E. *Twelve month follow-up of infants exposed to buprenorphine or methadone maintenance in pregnancy*. Oral presentation at the Combined Australasian Professional Society for Alcohol and Other Drugs and Cutting Edge Conference "Two Nations, Ten Cultures", Auckland, New Zealand, November 2007.

Whitham, J., Spurrier, N., Sawyer, M., Lopatko, O., & White, J. *Differences in Visual Evoked Potentials of 4 Month Old Infants Exposed to Buprenorphine or Methadone Maintenance Therapy During Pregnancy.* Oral presentation at the Annual Scientific Conference of the Australasian Professional Society for Alcohol and Other Drugs, Melbourne, November 2005.

Poster Presentations

JN Whitham, NJ Spurrier, MG Sawyer, PA Baghurst, JE Taplin. *Prenatal exposure to buprenorphine or methadone maintenance therapy: Differential effects on visual evoked potentials at four months of age*. The University of Adelaide Faculty of Health Sciences Postgraduate Research Expo, Adelaide September 2008

Appendix O. Note regarding content of Chapter 5

The content of Chapter 5 differs to that of my Master of Clinical Psychology thesis (Whitham, 2006) which utilised a sub-set of the current study sample (*N*=78). Details about prenatal exposure to other substances and early neonatal factors (including birth measurements and treatment for NAS) that may contribute to VEP latency were not available at that time and were therefore not included in the Master's thesis. This information has been incorporated in the statistical analyses in Chapter 5 of the current thesis which are of a more rigorous and sophisticated standard than those employed for the Master of Clinical Psychology thesis.

References

Abdel-Latif, M. E., Bajuk, B., Lui, K., & Oei, J. (2007). Short-term outcomes of infants of substance-

using mothers admitted to neonatal intensive care units in New South Wales and the

Australian Capital Territory. *Journal of Paediatrics and Child Health, 43*(3), 127-133. doi:

10.1111/j.1440-1754.2007.01031.x

Abindin, R. R. (1995). *Parenting Stress Index. Professional Manual* (Third ed.). Odessa, FL:

Psychological Assessment Resources, Inc.

Adams, E. H., Gfroerer, J. C., & Rouse, B. A. (1989). Epidemiology of substance abuse including

alcohol and cigarette smoking. *Annals of the New York Academy of Sciences, 562*, 14-20.

Algarin, C., Peirano, P., Garrido, M., Pizarro, F., & Lozoff, B. (2003). Iron deficiency anemia in

infancy: Long-lasting effects on auditory and visual system functioning. *Pediatric

Research, 53*(2), 217-223.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders,

Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association.

Anderson, P. (2006). Global use of alcohol, drugs and tobacco. *Drug and Alcohol Review, 25*(6),

489-502. doi: 10.1080/09595230600944446

Anstice, S., Strike, C. J., & Brands, B. (2009). Supervised Methadone Consumption: Client Issues

and Stigma. *Substance Use and Misuse, 44*(6), 794-808. doi:

doi:10.1080/10826080802483936

Aso, K., Watanabe, K., Negoro, T., Takaetsu, N., Furune, S., Takahashi, I., et al. (1988).

Developmental changes of pattern reversal visual evoked potentials. *Brain and

Development, 10*, 154-159.

Austin, M.-P., Hadzi-Pavlovic, D., Leader, L., Saint, K., & Parker, G. (2005). Maternal trait anxiety,

depression and life event stress in pregnancy: relationships with infant temperament.

Early Human Development, 81(2), 183-190. doi: DOI: 10.1016/j.earlhumdev.2004.07.001

Australian Drug Foundation. (2005a). Heroin Retrieved 28/09/05, 2005, from

http://www.druginfo.adf.org.au/article.asp?ContentID=heroin

Australian Drug Foundation. (2005b). Methadone Retrieved 28/09/05, 2005, from

http://www.druginfo.adf.org.au/article.asp?ContentID=methadone

Australian Institute of Health and Welfare. (2007). Statistics on drug use in Australia 2006 (Vol.).

Canberra: AIHW.

Australian Institute of Health and Welfare. (2008). 2007 National Drug Strategy Household Survey.

Detailed findings. Canberra: AIHW.

Australian Institute of Health and Welfare. (2010). National Opioid Pharmacotherapy Statistics

Annual Data collection: 2009 Report (Vol. Bulletin no.79. Cat. no. AUS 125). Canberra:

AIHW.

Australian Institute of Health and Welfare. (2011). 2010 National Drug Strategy Household Survey

Report. Canberra: AIHW.

Azuma, S. D., & Chasnoff, I. J. (1993). Outcome of Children Prenatally Exposed to Cocaine and

Other Drugs: A Path Analysis of Three-Year Data. *Pediatrics, 92*(3), 396-402.

Bauer, C. R., Shankaran, S., Bada, H. S., Lester, B., Wright, L. L., Krause-Steinrauf, H., et al. (2002).

The Maternal Lifestyle Study: Drug exposure during pregnancy and short-term maternal

outcomes. *American Journal of Obstetrics and Gynecology, 186*(3), 487-495.

Bauer, L. O. (1998). Effects of chronic opioid dependence and HIV-1 infection on pattern shift

visual evoked potentials. *Drug and Alcohol Dependence, 50*(2), 147-155.

Bayley, N. (1993). *Bayley Scales of Infant Development - Second Edition*. San Antonio: The

Psychological Corporation.

Bayley, N. (2006). *Bayley scales of infant and toddler development–Third edition*. San Antonio, TX:

Pearson Education, Inc.

Beckwith, L., Howard, J., Espinosa, M., & Tyler, R. (1999). Psychopathology, mother-child

interaction, and infant development: substance-abusing mothers and their offspring.

Development and Psychopathology, 11(4), 715-725.

Begg, S., Vos, T., Barker, B., Stevenson, C., Stanley, L., & Lopez, A. (2007). The burden of disease

and injury in Australia 2003. Canberra: Australian Institute of Health and Welfare.

Bell, G. L., & Lau, K. (1995). Perinatal and neonatal issues of substance abuse. *Pediatric Clinics in*

North America, 42(2), 261-281.

Berlin, C. M., McCarver, D. G., Notterman, D. A., Ward, R. M., Weismann, D. N., Wilson, G. S., et al.

(1998). Neonatal Drug Withdrawal. *Pediatrics, 101*(6), 1079-1088.

Bernstein, V. J., & Hans, S. L. (1994). Predicting the developmental outcome of two-year-old

children born exposed to methadone: Impact of social-environmental risk factors. *Journal*

of Clinical Child Psychology, 23, 349-359.

Bernstein, V. J., Jeremy, R. J., Hans, S. L., & Marcus, J. (1984). A longitudinal study of offspring

born to methadone-maintained women. II. Dyadic interaction and infant behavior at 4

months. *American Journal of Drug and Alcohol Abuse, 10*(2), 161-193.

Black, M., Schuler, M., & Nair, P. (1993). Prenatal drug exposure: neurodevelopmental outcome

and parenting environment. *Journal of Pediatric Psychology, 18*(5), 605-620.

Boffman, J., Clark, N., & Helsel, D. (1997). Can NCAST and HOME Assessment Scales be used with

Hmong refugees? *Pediatric Nursing, 23*(3), 235-244.

Bor, W., Najman, J. M., Anderson, M. J., O'Callaghan, M., Williams, G. M., & Behrens, B. C. (1997).

The relationship between low family income and psychological disturbance in young

children: an Australian longitudinal study. *Australian and New Zealand Journal of*

Psychiatry, 31, 664-675.

Borg, L., & Kreek, M. J. (1998). Pharmacology of Opiates In R. E. Tarter, R. T. Ammerman & P. J.

Ott (Eds.), *Handbook of Substance Abuse: Neurobehavioral Pharmacology* (pp. 331-362).

New York: Plenum Press.

Boughton, B. (2010). Buprenorphine Treatment Safer Than Methadone for Infants of Opiate-

Addicted Mothers. *Medscape Medical News*. Retrieved from

http://www.medscape.com/viewarticle/722213

Boyce, P., Stubbs, J., & Todd, A. (1993). The Edinburgh Postnatal Depression Scale: Validation for an Australian sample. *Australian and New Zealand Journal of Psychiatry, 27*, 472-476.

Bradley, R. H. (1994). The HOME Inventory: Review and reflections. *Advances in Child Development and Behavior, 25*, 241-288.

Brinciotti, M. (1994). Effects of chronic high serum levels of phenobarbital on evoked potentials in epileptic children. *Electroencephalography and Clinical Neurophysiology 92*(1), 11-16.

Buist, A., & Bilszta, J. (2005). The *beyondblue* National Postnatal Depression Program Prevention and Early Intervention 2001 – 2005 Final Report. Volume I: National Screening Program. In *beyondblue:* The National Depression Initiative. Melbourne, VIC.

Burns, L., Mattick, R. P., & Cooke, M. (2006). The use of record linkage to examine illicit drug use in pregnancy. [Article]. *Addiction, 101*(6), 873-882. doi: 10.1111/j.1360-0443.2006.01444.x

Caldwell, B. M., & Bradley, R. H. (1984). *Home Observation for Measurement of the Environment*. Little Rock, AR: University of Arkansas at Little Rock.

Carey, W. B., & McDevitt, S. C. (1978). Revision of the Infant Temperament Questionnaire. *Pediatrics, 61*(5), 735-739.

Carta, J. J., Atwater, J. B., Greenwood, C. R., McConnell, S. R., McEvoy, M. A., & Williams, R. (2001). Effects of cumulative prenatal substance exposure and environmental risks on children's developmental trajectories. *Journal of Clinical Child Psychology, 30*(3), 327-337.

Center for Substance Abuse Treatment. (2004). Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction *Treatment Improvement Protocol (TIP) Series 40.* Rockville, MD: Substance Abuse and Mental Health Services Administration.

Chan, A., Scott, J., Nguyen, A.-M., & Sage, L. (2007). Pregnancy Outcome in South Australia 2006 Adelaide: Pregnancy Outcome Unit, South Australian Department of Health.

Chander, G., & McCaul, M. E. (2003). Co-occurring psychiatric disorders in women with addictions. *Obstetrics and Gynecology Clinics of North America, 30*(3), 469-481.

Chang, G., Carroll, K. M., Behr, H. M., & Kosten, T. R. (1992). Improving treatment outcome in pregnant opiate-dependent women. *Journal of Substance Abuse Treatment, 9*, 327-330.

Chasnoff, I. J. (1985). Effects of maternal narcotic vs. nonnarcotic addiction on neonatal neurobehavior and infant development. *NIDA Research Monograph, 59*, 84-95.

Chasnoff, I. J., Anson, A. M. Y., Hatcher, R., Stenson, H., Iaukea, K. A. I., & Randolph, L. A. (1998). Prenatal Exposure to Cocaine and Other Drugs: Outcome at Four to Six Years. *Annals of the New York Academy of Sciences, 846*(1), 314-328. doi: 10.1111/j.1749-6632.1998.tb09748.x

Chasnoff, I. J., Burns, K., Burns, W. J., & Schnoll, S. (1986). Prenatal drug exposure: effects on neonatal and infant growth and development. *Neurobehavioral Toxicology and Teratology, 8*(4), 357-362.

Chasnoff, I. J., Hatcher, R., & Burns, W. J. (1982). Polydrug- and Methadone- Addicted Newborns: A Continuum of Impairment? *Pediatrics, 70*(2), 210.

Chasnoff, I. J., Schnoll, S. H., Burns, W. J., & Burns, K. (1984). Maternal nonnarcotic substance abuse during pregnancy: effects on infant development. *Neurobehavioral Toxicology and Teratology, 6*(4), 277-280.

Choo, R. E., Huestis, M. A., Schroeder, J. R., Shin, A. S., & Jones, H. E. (2004). Neonatal abstinence syndrome in methadone-exposed infants is altered by level of prenatal tobacco exposure. *Drug and Alcohol Dependence, 75*(3), 253-260.

Chutuape, M. A., Jasinski, D. R., Fingerhood, M. I., & Stitzer, M. L. (2001). One-, three-, and six-month outcomes after brief inpatient opioid detoxification. *American Journal of Drug and Alcohol Abuse, 27*(1), 19-44.

Cibis, G. W., & Fitzgerald, K. R. (1993). Vision testing in infants and nonresponsive children. In J. Dobbing (Ed.), *Lipids, Learning, and the Brain: Fats in Infant Formulas, Report of the 103rd Ross Conference on Pediatric Research* (pp. 104-109). Columbus, Ohio: Ross Laboratories.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Hillsdale, NJ: Erlbaum.

Condon, J. T., & Corkindale, C. J. (1998). The assessment of parent-to-infant attachment: Development of a self-report questionnaire instrument. *Journal of Reproductive and Infant Psychology, 16*(1), 57-77.

Cox, J., Holden, J., & Sagovsky, R. (1987). Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *The British Journal of Psychiatry, 150*(6), 782-786.

Czerkes, M. (2010). *Buprenorphine versus Methadone Treatment for Opiate Addiction in Pregnancy: An Evaluation of Neonatal Outcomes*. Paper presented at the American Congress of Obstetricians and Gynecologists (ACOG) 58th Annual Clinical Meeting, San Francisco, CA. http://www.medscape.com/viewarticle/722213

Dashe, J. S., Jackson, G. L., Olscher, D. A., Zane, E. H., & Wendel, G. D. (1998). Opioid Detoxification in Pregnancy. *Obstetrics and Gynecology, 92*, 854-858.

Davids, E., & Gastpar, M. (2004). Buprenorphine in the treatment of opioid dependence. *European Neuropsychopharmacology, 14*, 209-216.

Davis, D. D., & Templer, D. I. (1988). Neurobehavioral functioning in children exposed to narcotics in utero. *Addictive Behaviors, 13*, 275-283.

Dawe, S., & Harnett, P. (2007). Reducing potential for child abuse among methadone-maintained parents: Results from a randomized controlled trial. *Journal of Substance Abuse Treatment, 32*(4), 381-390.

Dawe, S., Harnett, P., Rendalls, V., & Staiger, P. (2003). Improving family functioning and child outcomes in methadone maintained families: the Parents Under Pressure programme. *Drug and Alcohol Review, 22*, 299-307.

Degenhardt, L., Hall, W., Warner-Smith, M., & Lynskey, M. (2004). Illicit Drug Use. In M. Ezzati, A. Lopez, A. Rodgers & C. J. L. Murray (Eds.), *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors* (Vol. 1, pp. 1109-1170). Geneva: World Health Organisation.

Dempsey, J. P., Back, S. E., Waldrop, A. E., Jenkins, L., & Brady, K. T. (2008). The Influence of

Monetary Compensation on Relapse among Addicted Participants: Empirical vs. Anecdotal

Evidence. *American Journal on Addictions, 17*(6), 488-490. doi:

doi:10.1080/10550490802408423

Di Russo, F., Martínez, A., Sereno, M. I., Pitzalis, S., & Hillyard, S. A. (2002). Cortical sources of the

early components of the visual evoked potential. *Human Brain Mapping, 15*(2), 95-111.

doi: 10.1002/hbm.10010

Dickert, N., & Grady, C. (1999). What's the Price of a Research Subject? Approaches to Payment

for Research Participation. *New England Journal of Medicine, 341*(3), 198-203. doi:

10.1056/nejm199907153410312

Dixon, S. D., Coen, R. W., & Crutchfield, S. (1987). Visual Dysfunction in cocaine-exposed infants.

Pediatric Research, 21, 359A.

Doberczak, T. M., Kandall, S. R., & Wilets, I. (1991). Neonatal opiate abstinence syndrome in term

and preterm infants. *The Journal of Pediatrics, 118*(6), 933-937.

Dole, V. P., & Nyswander, M. (1965). A Medical Treatment for Diacetylmorphine (Heroin)

Addiction: A Clinical Trial With Methadone Hydrochloride. *Journal of the American

Medical Association, 193*(8), 646-650. doi: 10.1001/jama.1965.03090080008002

Donath, S. (2001). The validity of the 12-item General Health Questionnaire in Australia: a

comparison between three scoring methods. *Australian and New Zealand Journal of

Psychiatry, 35*, 231-235.

Dunlop, A. J., Panjari, M., O'Sullivan, H., Henschke, P., Love, V., Ritter, A., et al. (2003). Clinical

guidelines for the use of buprenorphine in pregnancy. Melbourne: Turning Point Alcohol

and Drug Centre.

Eberhard-Gran, M., Eskild, A., Tambs, K., Opjordsmoen, S., & Samuelsen, S. O. (2001). Review of

validation studies of the Edinburgh Postnatal Depression Scale. *Acta Psychiatrica

Scandinavica, 104*, 243-249.

Ebner, N., Rohrmeister, K., Winklbaur, B., Baewert, A., Jagsch, R., Peternell, A., et al. (2007). Management of neonatal abstinence syndrome in neonates born to opioid maintained women. *Drug and Alcohol Dependence, 87*(2-3), 131-138.

Edhborg, M., Seimyr, L., Lundh, W., & Widstrom, A. M. (2000). Fussy child--difficult parenthood? Comparisons between families with a 'depressed' mother and non-depressed mother 2 months postpartum. *Journal of Reproductive and Infant Psychology, 18*(3), 225.

Edwards, A. L. (1979). *Multiple Regression and the Analysis of Variance and Covariance*. San Francisco: W.H. Freeman and Company.

Edwards, B., Galletly, C., Semmler-Booth, T., & Dekker, G. (2008). Does antenatal screening for psychosocial risk factors predict postnatal depression? A follow-up study of 154 women in Adelaide, South Australia. *Australian and New Zealand Journal of Psychiatry, 42*(1), 51 - 55.

Eklund, M., Bengtsson-Tops, A., & Lindstedt, H. (2007). Construct and discriminant validity and dimensionality of the Interview Schedule for Social Interaction (ISSI) in three psychiatric samples. *Nordic Journal of Psychiatry, 61*(3), 182-188.

Ellman, L. M., Schetter, C. D., Hobel, C. J., Chicz-DeMet, A., Glynn, L. M., & Sandman, C. A. (2008). Timing of fetal exposure to stress hormones: Effects on newborn physical and neuromuscular maturation. *Developmental Psychobiology, 50*(3), 232-241. doi: 10.1002/dev.20293

Essex, M. J., Klein, M. H., Miech, R., & Smider, N. A. (2001). Timing of initial exposure to maternal major depression and children's mental health symptoms in kindergarten. *British Journal of Psychiatry, 179*, 151-156.

Everitt, B. J., & Robbins, T. W. (1997). Central cholinergic systems and cognition. *Annual Review of Psychology, 48*(1), 649.

Farid, W. O., Dunlop, S. A., Tait, R. J., & Hulse, G. K. (2008). The Effects of Maternally Administered Methadone, Buprenorphine and Naltrexone on Offspring: Review of Human and Animal Data. *Current Neuropharmacology, 6*(2), 125-150. doi: 10.2174/157015908784533842

Feldman, R., & Eidelman, A. I. (2003). Direct and indirect effects of breast milk on the

    neurobehavioral and cognitive development of premature infants. *Developmental*

    Psychobiology, 43(2), 109-119.

Festinger, D. S., Marlowe, D. B., Croft, J. R., Dugosh, K. L., Mastro, N. K., Lee, P. A., et al. (2005). Do

    research payments precipitate drug use or coerce participation? *Drug and Alcohol*

    Dependence, 78(3), 275-281.

Festinger, D. S., Marlowe, D. B., Dugosh, K. L., Croft, J. R., & Arabia, P. L. (2008). Higher magnitude

    cash payments improve research follow-up rates without increasing drug use or perceived

    coercion. *Drug and Alcohol Dependence, 96*(1-2), 128-135.

Finch, B. K., Vega, W. A., & Kolody, B. (2001). Substance use during pregnancy in the state of

    California, USA. *Social Science and Medicine, 52*(4), 571-583.

Finnegan, L. P. (1990). Neonatal Abstinence Syndrome. In N. M. Nelson (Ed.), *Current Therapy in*

    Neonatal-Perinatal Medicine- 2 (pp. 314-320). Toronto: B.C. Decker Inc.

Finnegan, L. P., Connaughton, J. F. J., Kron, R. E., & Emich, J. P. (1975). Neonatal abstinence

    syndrome: assessment and management. *Addictive Diseases, 2*(1-2), 141-158.

Finnegan, L. P., & Kandall, S. R. (1997). Maternal and neonatal effects of alcohol and drugs. In J.

    Lowinson, P. Ruiz, R. B. Millman & J. G. Langrod (Eds.), *Substance Abuse: A Comprehensive*

    Textbook (3rd ed., pp. 513-534). Baltimore: Williams and Wilkins.

Finnegan, L. P., Oehlberg, S. M., Regan, D. O. M., & Rudrauff, M. E. (1981). Evaluation of

    parenting, depression and violence profiles in methadone maintained women. *Child*

    Abuse and Neglect, 5(3), 267-273.

Fischer, G., Johnson, R. E., Eder, H., Jagsch, R., Peternell, A., Weninger, M., et al. (2000).

    Treatment of opioid-dependent pregnant women with buprenorphine. *Addiction, 95*(2),

    239-245.

Fischer, G., Ortner, R., Rohrmeister, K., Jagsch, R., Baewert, A., Langer, M., et al. (2006).

    Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy

    comparison study. *Addiction, 101*(2), 275-281.

Frank, D. A., Jacobs, R. R., Beeghly, M., Augustyn, M., Bellinger, D., Cabral, H., et al. (2002). Level of Prenatal Cocaine Exposure and Scores on the Bayley Scales of Infant Development: Modifying Effects of Caregiver, Early Intervention, and Birth Weight. *Pediatrics, 110*(6), 1143-1152. doi: 10.1542/peds.110.6.1143

Fried, P. A. (1989). Postnatal consequences of maternal marijuana use in humans. *Annals of the New York Academy of Sciences, 562*, 123-132.

Fried, P. A., O'Connell, C. M., & Watkinson, B. (1992). 60- & 72- month follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol: Cognitive and language assessment. *Developmental and Behavioral Pediatrics, 13*, 383-391.

Fudala, P. J., & O'Brien, C. (2005). Buprenorphine for the treatment of opioid addiction. In J. Lowinson, P. Ruiz, R. B. Millman & J. G. Langrod (Eds.), *Substance Abuse: A Comprehensive Textbook* (4th ed.). Philadelphia: Lippincott, Williams & Wilkins.

Fullard, W., McDevitt, S. C., & Carey, W. B. (1984). Assessing Temperament in One-to Three-Year-Old Children. *Journal of Pediatric Psychology, 9*(2), 205-217. doi: 10.1093/jpepsy/9.2.205

Gagnon, S. G., & Nagle, R. J. (2000). Comparison of the Revised and Original Versions of the Bayley Scales of Infant Development. *School Psychology International, 21*(3), 293-305. doi: 10.1177/0143034300213006

García-Alix, A., Sáenz-de Pipaón, M., Martínez, M., Salas-Hernández, S., & Quero, J. (2004). Ability of neonatal head circumference to predict long-term neurodevelopmental outcome. *Revista de Neurologia, 39*(6), 548-554.

Gibson, F. L., Ungerer, J. A., Leslie, G. I., Saunders, D. M., & Tennant, C. C. (1998). Development, behaviour and temperament: a prospective study of infants conceived through in-vitro fertilization. *Human Reproduction, 13*(6), 1727-1732. doi: 10.1093/humrep/13.6.1727

Goel, N., Beasley, D., Rajkumar, V., & Banerjee, S. (2010). Perinatal outcome of illicit substance use in pregnancy—comparative and contemporary socio-clinical profile in the UK. *European Journal of Pediatrics, 170*(2), 199-205. doi: 10.1007/s00431-010-1284-6

Gold, M. S., & Johnson, C. R. (1998). Psychological and Psychiatric consequences of opiates In R. E. Tarter, R. T. Ammerman & P. J. Ott (Eds.), *Handbook of Substance Abuse : Neurobehavioral Pharmacology* (pp. 363-370). New York: Plenum Press.

Goldberg, D. P., Gater, R., Sartorius, N., Ustun, T. B., Piccinelli, M., Gureje, O., et al. (1997). The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychological Medicine, 27*, 191-197.

Goldberg, D. P., & Hillier, V. F. (1979). A scaled version of the General Health Questionnaire. *Psychological Medicine, 9*, 139-145.

Gomez-Flores, R., & Weber, R. J. (2000). Differential effects of buprenorphine and morphine on immune and neuroendocrine functions following acute administration in the rat mesencephalon periaqueductal gray. *Immunopharmacology, 48*(2), 145-156. doi: Doi: 10.1016/s0162-3109(00)00198-3

Gordon, A. L. (2006). *Buprenorphine and Methadone in pregnancy: effects on the mother, fetus and neonate.* Doctor of Philosophy, The University of Adelaide, Adelaide.

Grace, S. L., Evindar, A., & Stewart, D. E. (2003). The effect of postpartum depression on child cognitive development and behavior: a review and critical analysis of the literature. *Archives of Women's Mental Health, 6*(4), 263-274.

Hall, W. D., Ross, J. E., Lynskey, M. T., Law, M. G., & Degenhardt, L. J. (2000). How many dependent heroin users are there in Australia? *Medical Journal of Australia, 173*, 528-531.

Hamilton, R., McGlone, L., MacKinnon, J. R., Russell, H. C., Bradnam, M. S., & Mactier, H. (2010). Ophthalmic, clinical and visual electrophysiological findings in children born to mothers prescribed substitute methadone in pregnancy. *British Journal of Ophthalmology, 94*(6), 696-700. doi: 10.1136/bjo.2009.169284

Hans, S. L. (1989). Developmental consequences of prental exposure to methadone. *Annals of the New York Academy of Sciences, 562*, 195-207.

Hans, S. L., Bernstein, V. J., & Henson, L. G. (1999). The role of psychopathology in the parenting of drug-dependent women. *Development and Psychopathology, 11*(4), 957-977.

Hansen, R. L., Struthers, J. M., & Gospe, S. M. (1993). Visual evoked potentials and visual processing in stimulant drug-exposed infants. *Developmental Medicine and Child Neurology, 35*, 798-805.

Henderson, S., Duncan-Jones, P., Byrne, D. G., & Scott, R. (1980). Measuring social relationships. The Interview Schedule for Social Interaction. *Psychological Medicine, 10*, 723-734.

Henry-Edwards, S., Gowing, L., White, J., Ali, R., Bell, J., Brough, R., et al. (2003). Clinical Guidelines and Procedures for the Use of Methadone in the Maintenance Treatment of Opioid Dependence: Australian Government Department of Health and Aging.

Herlenius, E., & Lagercrantz, H. (2004). Development of neurotransmitter systems during critical periods. *Experimental Neurology, 190*(Supplement 1), 8-21. doi: DOI: 10.1016/j.expneurol.2004.03.027

Herrero, M.-T., Barcia, C., & Navarro, J. (2002). Functional anatomy of thalamus and basal ganglia. *Child's Nervous System, 18*(8), 386-404. doi: 10.1007/s00381-002-0604-1

Hipwell, A. E., Goossens, F. A., Melhuish, E. C., & Kumar, R. (2000). Severe maternal psychopathology and infant-mother attachment. *Development and Psychopathology, 12*(2), 157-175.

Hoare, J. (2009). Drug misuse declared: findings from the 2008/09 British Crime Survey—England and Wales Retrieved 1 November 2010, from http://rds.homeoffice.gov.uk/rds/pdfs09/hosb1209.pdf.

Hodgson, B. (1999). *Opium: A Portrait of the Heavenly Demon*. Vancouver: Greystone Books.

Holmes, G. L., Harden, C., Liporace, J., & Gordon, J. (2007). Postnatal concerns in children born to women with epilepsy. *Epilepsy and Behavior, 11*(3), 270-276.

House of Representatives Standing Committee on Health and Ageing. (2007). *The Best Start: Report on the inquiry into the health benefits of breastfeeding*. Canberra: Commonwealth of Australia Retrieved from http://www.aph.gov.au/house/committee/haa/breastfeeding/report.htm.

Hunt, R. W., Tzioumi, D., Collins, E., & Jeffery, H. E. (2008). Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Human Development, 84*, 29-35.

Huntington, L., Hans, S. L., & Zesking, P. S. (1990). The relations among cry characteristics, demograpphic variables, and developmental test scores in infants prenatally exposed to methadone. *Infant Behavior and Development, 13*, 533-538.

Hutchings, D. E., Zmitrovich, A., Brake, S. C., Malowany, D., Church, S., & Nero, T. J. (1992). Prenatal administration of methadone using the osmotic minipump: Effects on maternal and offspring toxicity, growth, and behavior in the rat. *Neurotoxicology and Teratology, 14*(1), 65-71. doi: Doi: 10.1016/0892-0362(92)90030-e

Hutchings, D. E., Zmitrovich, A. C., Hamowy, A. S., & Liu, P.-V. R. (1995). Prenatal administration of buprenorphine using the osmotic minipump: A preliminary study of maternal and offspring toxicity and growth in the rat. *Neurotoxicology and Teratology, 17*(4), 419-423.

Iinuma, K., Lombroso, C. T., & Matsumiya, Y. (1997). Prognostic value of visual evoked potentials (VEP) in infants with visual inattentiveness. *Electroencephalography and Clinical Neurophysiology, 104*(2), 165-170.

Jaffe, J. H., Knapp, C. M., & Ciraulo, D. A. (1997). Opiates: Clinical Aspects. In J. H. Lowinson, P. Ruiz, R. B. Millman & J. G. Langrod (Eds.), *Substance Abuse: A Comprehensive Textbook* (3rd ed., pp. 158-166). Baltimore: Williams and Wilkins.

Jarvis, M. A., & Schnoll, S. (1995). Methadone use during pregnancy. *NIDA Research Monograph, 149*, 58-77.

Jasinski, D. R., Pevnick, J. S., & Griffith, J. H. (1978). Human Pharmacology and Abuse Potential of the Analgesic Buprenorphine: A Potential Agent for Treating Narcotic Addiction *Archives of General Psychiatry, 35*(4), 501-516.

Jeremy, R. J., & Bernstein, V. J. (1984). Dyads at risk: methadone-maintained women and their four-month-old infants. *Child Development, 55*(4), 1141-1154.

Jeremy, R. J., & Hans, S. L. (1985). Behavior of neonates exposed in utero to methadone as assessed on the Brazelton Scale. *Infant Behavior and Development, 8*, 323-336.

Johnson, H. L., Glassman, M. B., Fiks, K. B., & Rosen, T. S. (1987). Path analysis of variables affecting 36-month outcome in a population of multi-risk children. *Infant Behavior and Development, 10*, 451-465.

Johnson, H. L., Glassman, M. B., Fiks, K. B., & Rosen, T. S. (1990). Resilient children: individual differences in developmental outcome of children born to drug abusers. *Journal of Genetic Psychology, 151*(4), 523-539.

Johnson, H. L., & Rosen, T. S. (1982). Prenatal methadone exposure: effects on behavior in early infancy. *Pediatric Pharmacology, 2*(2), 113-120.

Johnson, R. E., Jones, H. E., & Fischer, G. (2003). Use of buprenorphine in pregnancy: patient management and effects on the neonate. *Drug and Alcohol Dependence, 70*(2, Supplement 1), S87-S101.

Johnson, R. E., Jones, H. E., Jasinski, D. R., Svikis, D. S., Haug, N. A., Jansson, L. M., et al. (2001). Buprenorphine treatment of pregnant opioid-dependent women: maternal and neonatal outcomes. *Drug and Alcohol Dependence, 63*(1), 97-103.

Johnson, R. E., Strain, E. C., & Amass, L. (2003). Buprenorphine: How to use it right. *Drug and Alcohol Dependence, 70*, S59-S77.

Jones, H. E., Heil, S. H., O'Grady, K. E., Martin, P. R., Kaltenbach, K., Coyle, M. G., et al. (2009). Smoking in Pregnant Women Screened for an Opioid Agonist Medication Study Compared to Related Pregnant and Non-Pregnant Patient Samples. *American Journal of Drug & Alcohol Abuse, 35*(5), 375-380. doi: 10.1080/00952990903125235

Jones, H. E., Johnson, R. E., Jasinski, D. R., O'Grady, K. E., Chisholm, C. A., Choo, R. E., et al. (2005). Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug and Alcohol Dependence, 79*(1), 1-10.

Jones, H. E., Kaltenbach, K., Heil, S. H., Stine, S. M., Coyle, M. G., Arria, A. M., et al. (2010). Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure. *New England Journal of Medicine, 363*(24), 2320-2331. doi: doi:10.1056/NEJMoa1005359

Jones, H. E., Kaltenbach, K., & O'Grady, K. E. (2009). The complexity of examining developmental

outcomes of children prenatally exposed to opiates. A response to the Hunt et al. Adverse

neurodevelopmental outcome of infants exposed to opiates in-utero. Early Human

Development (2008, 84, 29-35). *Early Human Development, 85*(4), 271-272. doi: DOI:

10.1016/j.earlhumdev.2008.10.001

Jones, H. E., O'Grady, K. E., Malfi, D., & Tuten, M. (2008). Methadone Maintenance vs. Methadone

Taper During Pregnancy: Maternal and Neonatal Outcomes. [Article]. *American Journal on

Addictions, 17*(5), 372-386. doi: 10.1080/10550490802266276

Kahila, H., Kivitie-Kallio, S., Halmesmaki, E., Valanne, L., & Autti, T. (2007). Brain magnetic

resonance imaging of infants exposed prenatally to buprenorphine. *Acta Radiologica,

48*(2), 228-231.

Kahila, H., Saisto, T., Kivitie-Kallio, S., Haukkamaa, M., & Halmesmaki, E. (2007). A prospective

study on buprenorphine use during pregnancy: effects on maternal and neonatal

outcome. *Acta Obstetricia et Gynecologica Scandinavica, 86*(2), 185 - 190.

Kakko, J., Heilig, M., & Sarman, I. (2008). Buprenorphine and methadone treatment of opiate

dependence during pregnancy: Comparison of fetal growth and neonatal outcomes in two

consecutive case series. *Drug and Alcohol Dependence, 96*(1-2), 69-78.

Kaltenbach, K. (1994). Effects of in-utero opiate exposure: new paradigms for old questions. *Drug

and Alcohol Dependence, 36*(2), 83-87.

Kaltenbach, K., Berghella, V., & Finnegan, L. (1998). Opioid dependence during pregnancy: Effects

and management. *Obstetrics and Gynecology Clinics of North America, 25*(1), 139-151.

Kaltenbach, K., & Finnegan, L. P. (1986). Neonatal abstinence syndrome, pharacotherapy and

developmental outcome. *Neurobehavioral Toxicology and Teratology, 8*(4), 353-355.

Kaltenbach, K., & Finnegan, L. P. (1987). Perinatal and developmental outcome of infants exposed

to methadone in-utero. *Neurotoxicology and Teratology, 9*(4), 311-313.

Kandall, S. R. (1996). *Substance and Shadow: Women and Addiction in the United States*.

Cambridge, MA: Harvard University Press.

Kandall, S. R., Albin, S., Gartner, L. M., Lee, K.-S., Eidelman, A., & Lowinson, J. (1977). The narcotic-dependent mother: Fetal and neonatal consequences. *Early Human Development, 1*(2), 159-169. doi: Doi: 10.1016/0378-3782(77)90017-2

Kandall, S. R., Albin, S., Lowinson, J., Berle, B., Eidelman, A. I., & Gartner, L. M. (1976). Differential effects of maternal heroin and methadone use on birthweight. *Pediatrics, 58*(5), 681-685.

Kandall, S. R., Doberczak, T. M., Jantunen, M., & Stein, J. (1999). The methadone maintained pregnancy. *Clinics in Perinatology, 26*(1), 173-183.

Kato, T., & Watanabe, K. (2006). Visual evoked potential in the newborn: Does it have predictive value? *Seminars in Fetal and Neonatal Medicine, 11*(6), 459-463.

Kayemba-Kay's, S., & Laclyde, J. P. (2003). Buprenorphine withdrawal syndrome in newborns: a report of 13 cases. *Addiction, 98*(11), 1599-1604.

Kennare, R., Heard, A., & Chan, A. (2005). Substance use during pregnancy: risk factors and obstetric and perinatal outcomes in South Australia. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 45*(3), 220-225. doi: 10.1111/j.1479-828X.2005.00379.x

Kessler, R. C., Nelson, C. B., McGonagle, K. A., Edlund, M. J., Frank, R. G., & Leaf, P. J. (1996). The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization. *American Journal of Orthopsychiatry, 66*(1), 17-31.

Khedr, E. M. H., Farghaly, W. M. A., Amry, S.-E.-D., & Osman, A. A. A. (2004). Neural maturation of breastfed and formula-fed infants. *Acta Paediatrica, 93*, 734-738.

Kolb, B., & Wishaw, I. Q. (1996). *Fundamentals of Human Neuropsychology* (Fourth ed.). New York: W.H. Freeman and Company.

Konijnenberg, C., & Melinder, A. (2011). Prenatal exposure to methadone and buprenorphine: A review of the potential effects on cognitive development. *Child Neuropsychology*. Retrieved from doi:10.1080/09297049.2011.553591

Koren, G., Matsui, D., Einarson, A., Knoppert, D., & Steiner, M. (2005). Is maternal use of selective serotonin reuptake inhibitors in the third trimester of pregnancy harmful to neonates? *Canadian Medical Association Journal, 172*(11), 1457-1459.

Kosten, T. R., Morgan, C., & Kosten, T. A. (1990). Depressive symptoms during buprenorphine

treatment of opioid abusers. *Journal of Substance Abuse Treatment, 7*(1), 51-54.

Lacroix, I., Berrebi, A., Chaumerliac, C., Lapeyre-Mestre, M., Montastruc, J. L., & Damase-Michel,

C. (2004). Buprenorphine in pregnant opioid-dependent women: first results of a

prospective study. *Addiction, 99*(2), 209-214.

Laken, M. P., McComish, J. F., & Ager, J. (1997). Predictors of prenatal substance use and birth

weight during outpatient treatment. *Journal of Substance Abuse Treatment, 14*(4), 359-

366.

Laws, P. J., & Hilder, L. (2008). Australia's mothers and babies 2006. Perinatal statistics series no.

22. Cat. no. PER 46. Sydney: AIHW National Perinatal Statistics Unit.

Lejeune, C., Simmat-Durand, L., Gourarier, L., & Aubisson, S. (2006). Prospective multicenter

observational study of 260 infants born to 259 opiate-dependent mothers on methadone

or high-dose buprenorphine substitution. *Drug and Alcohol Dependence, 82*(3), 250-257.

Lester, B. M., ElSohly, M., Wright, L. L., Smeriglio, V. L., Verter, J., Bauer, C. R., et al. (2001). The

Maternal Lifestyle Study: Drug Use by Meconium Toxicology and Maternal Self-Report.

Pediatrics, 107(2), 309-317. doi: 10.1542/peds.107.2.309

Levy, M., & Spino, M. (1993). Neonatal withdrawal syndrome: associated drugs and

pharmacologic management. *Pharmacotherapy, 13*(3), 202-211.

Lichtblau, L., & Sparber, S. B. (1981). Opiate Withdrawal in Utero Increases Neonatal Morbidity in

the Rat. *Science, 212*(4497), 943-945.

Lifschitz, M. H., Wilson, G. S., Smith, E. O. B., & Desmond, M. M. (1983). Fetal and postnatal

growth of children born to narcotic-dependent women. *The Journal of Pediatrics, 102*(5),

686-691. doi: Doi: 10.1016/s0022-3476(83)80234-0

Lifschitz, M. H., Wilson, G. S., Smith, E. O. B., & Desmond, M. M. (1985). Factors Affecting Head

Growth and Intellectual Function in Children of Drug Addicts. *Pediatrics, 75*(2), 269-274.

Ling, W., & Wesson, D. R. (2003). Clinical efficacy of buprenorphine: comparisons to methadone

and placebo. *Drug and Alcohol Dependence, 70*(2, Supplement 1), S49-S57.

Lintzeris, N., Clark, N., Winstock, A., Dunlop, A., Muhleisen, P., Gowing, L., et al. (2006). National

Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Dependence:

Commonwealth of Australia.

Lodge, A., Marcus, M., & Ramer, C. (1975). Behavioral and Electrophysiological characteristics of

the addicted neonate. *Addictive Diseases, 2*(2), 235-255.

Lowinson, J. H., Marion, I., Joseph, H., Langrod, J. G., Salsitz, E. A., Payte, J. T., et al. (2005).

Methadone Maintenance. In J. H. Lowinson, P. Ruiz, R. B. Millman & J. G. Langrod (Eds.),

Substance Abuse: A Comprehensive Textbook (4th ed.). Philadelphia: Lippincott, Williams

& Wilkins.

Lozoff, B., Park, A. M., Radan, A. E., & Wolf, A. W. (1995). Using the HOME inventory with infants

in Costa Rica. *International Journal of Behavioral Development 18*(2), 277-295.

Lundgren, L. M., Fitzgerald, T., Young, N., Amodeo, M., & Schilling, R. F. (2007). Medication

assisted drug treatment and child well-being. *Children and Youth Services Review, 29*(8),

1051-1069.

Luty, J., Nikolaou, V., & Bearn, J. (2003). Is opiate detoxification unsafe in pregnancy? *Journal of

Substance Abuse Treatment, 24*(4), 363-367. doi: 10.1016/s0740-5472(03)00035-7

Madrid, M., & Crognale, M. A. (2000). Long-term maturation of visual pathways. *Visual

Neuroscience, 17*, 831-837.

Makrides, M., Neumann, M. A., & Gibson, R. A. (2001). Perinatal characteristics may influence the

outcome of visual acuity. *Lipids, 36*(9), 897-900.

Makrides, M., Neumann, M. A., Jeffrey, B., Lien, E. L., & Gibson, R. A. (2000). A randomized trial of

different ratios of linoleic to a-linolenic acid in the diet of term infants: effects on visual

function and growth. *American Journal of Clinical Nutrition, 71*, 120-129.

Marcus, J., Hans, S., & Jeremy, R. (1984). A longitudinal study of offspring born to methadone-

maintained women. III. Effects of multiple risk factors on development at 4, 8, and 12

months. *American Journal of Drug and Alcohol Abuse, 10*, 195-207.

Marquet, P., Chevrel, J., Lavignasse, P., Merle, L., & Lachatre, G. (1997). Buprenorphine withdrawal syndrome in a newborn. *Clinical Pharmacology and Therapeutics, 62*(5), 569-571.

Mathers, C., Vos, T., & Stevenson, C. (1999). The burden of disease and injury in Australia. Canberra: Australian Institute of Health and Welfare.

Matsunaga, M. (2006). *Familywise Alpha Adjustment Returns: The Case for a Disputed Procedure.* Paper presented at the the annual meeting of the International Communication Association; Jun 16, Dresden International Congress Centre, Dresden, Germany.

Matthey, S., Henshaw, C., Elliott, S., & Barnett, B. (2006). Variability in use of cut-off scores and formats on the Edinburgh Postnatal Depression Scale: Implications for clinical and research practice. *Archives of Women's Mental Health, 9*(6), 309-315.

Mattick, R. P., Kimber, J., Breen, C., & Davoli, M. (2003). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *The Cochrane Database of Systematic Reviews*(Issue 2), Art. No.: CD002207.pub002202. DOI: 002210.001002/14651858.CD14002207.pub14651852.

Mayes, L. C., Cicchetti, D., Acharyya, S., & Zhang, H. (2003). Developmental Trajectories of Cocaine-and-Other-Drug-Exposed and Non-Cocaine-Exposed Children. *Journal of Developmental and Behavioral Pediatrics, 24*(5), 323-335.

McBride, O., Teesson, M., Slade, T., Hasin, D., Degenhardt, L., & Baillie, A. (2009). Further evidence of differences in substance use and dependence between Australia and the United States. *Drug and Alcohol Dependence, 100*(3), 258-264. doi: DOI: 10.1016/j.drugalcdep.2008.10.011

McCulloch, D. L., McGlone, L., Bradnam, M. S., Hepburn, M., Hamilton, R., Borland, W., et al. (2007). *Flash and Flicker VEPs in newborn term infants of drug-misusing mothers.* Paper presented at the 45th International Symposium International Society for Clinical Electrophysiology of Vision, Hyderabad, India.

McCulloch, D. L., Orbach, H., & Skarf, B. (1999). Maturation of the pattern-reversal VEP in human

infants: a theoretical framework. *Vision Research, 39*, 3673-3680.

McGlone, L., Mactier, H., Hamilton, R., Bradnam, M. S., Boulton, R., Borland, W., et al. (2008).

Visual evoked potentials in infants exposed to methadone in utero. *Archives of Disease in

Childhood, 93*(9), 784-786. doi: 10.1136/adc.2007.132985

McMahon, C. A., Barnett, B., Kowalenko, N., Tennant, C., & Don, N. (2001). Postnatal depression,

anxiety and unsettled infant behaviour. *Australian and New Zealand Journal of Psychiatry,

35*, 581-588.

Meador, K. J., Baker, G., Cohen, M. J., Gaily, E., & Westerveld, M. (2007). Cognitive/behavioral

teratogenetic effects of antiepileptic drugs. *Epilepsy and Behavior 11*(3), 292-302.

Messinger, D. S., Bauer, C. R., Das, A., Seifer, R., Lester, B. M., Lagasse, L. L., et al. (2004). The

Maternal Lifestyle Study: Cognitive, Motor, and Behavioral Outcomes of Cocaine-Exposed

and Opiate-Exposed Infants Through Three Years of Age. *Pediatrics, 113*(6), 1677-1685.

doi: 10.1542/peds.113.6.1677

Mikhail, M. S., Youchah, J., DeVore, N., Ho, G. Y., & Anyaegbunam, A. (1995). Decreased maternal-

fetal attachment in methadone-maintained pregnant women: a preliminary study. *Journal

of the Association for Academic Minority Physicians, 6*(3), 112-114.

Miller-Lewis, L. R., Baghurst, P. A., Sawyer, M. G., Prior, M. R., Clark, J. J., Arney, F. M., et al.

(2006). Early childhood externalising behaviour problems: Child, parenting, and family-

related predictors over time. *Journal of Abnormal Child Psychology, 34*(891-906).

Morse, B., Weiner, L., & Garrido, P. (1989). Focusing prevention of fetal alcohol syndrome on

women at risk. *Annals of the New York Academy of Sciences, 562*, 342-343.

Moskowitz, A., & Sokol, S. (1983). Developmental changes in the human visual system as reflected

by the latency of the pattern reversal VEP. *Electroencephalography and Clinical

Neurophysiology, 56*, 1-15.

Mulvihill, A., Cackett, P., George, N., & Fleck, B. (2007). Nystagmus secondary to drug exposure in

utero. *British Journal of Ophthalmology, 91*(5), 613-615.

Murphy, S., & Irwin, J. (1992). Living with the dirty secret: problems of disclosure for methadone maintenance clients. *Journal of Psychoactive Drugs, 24*(3), 257-264.

Murray, L., & Carothers, A. D. (1990). The Validation of the Edinburgh Post-natal Depression Scale on a community sample. *British Journal of Psychiatry, 157*, 288-290.

Murray, L., Fiori-Cowley, A., Hooper, R., & Cooper, P. (1996). The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. *Child Development, 67*, 2512-2526.

Nair, P., Schuler, M. E., Black, M. M., Kettinger, L., & Harrington, D. (2003). Cumulative environmental risk in substance abusing women: early intervention, parenting stress, child abuse potential and child development. *Child Abuse and Neglect, 27*(9), 997-1017.

Najman, J. M., Williams, G. M., Nikles, J., Spence, S. U. E., Bor, W., O'Callaghan, M., et al. (2000). Mothers' Mental Illness and Child Behavior Problems: Cause-Effect Association or Observation Bias? *Journal of the American Academy of Child & Adolescent Psychiatry, 39*(5), 592-602. doi: 10.1097/00004583-200005000-00013

Nanovskaya, T., Deshmukh, S., Brooks, M., & Ahmed, M. S. (2002). Transplacental Transfer and Metabolism of Buprenorphine. *Journal of Pharmacology and Experimental Therapeutics, 300*(1), 26-33.

National Health and Medical Research Council. (2001). Australian alcohol guidelines: Health risks and benefits (pp. 1-128). Canberra: National Health and Medical Research Council; Commonwealth of Australia.

Nekhayeva, I. A., Nanovskaya, T. N., Deshmukh, S. V., Zharikova, O. L., Hankins, G. D. V., & Ahmed, M. S. (2005). Bidirectional transfer of methadone across human placenta. *Biochemical Pharmacology, 69*(1), 187-197.

New South Wales Department of Health. (2006a). Background papers to the National clinical guidelines for the management of drug use during pregnancy, birth and the early development years of the newborn. Sydney: Commonwealth of Australia.

New South Wales Department of Health. (2006b). National clinical guidelines for the management of drug use during pregnancy, birth and the early development years of the newborn. Sydney: Commonwealth of Australia.

Northern and Yorkshire Public Health Observatory. (2002). *Drug misuse in pregnancy in the Northern and Yorkshire Region. Occasional Paper No.6.*: Retrieved from http://www.dur.ac.uk/ne.pho/view_file.php?c=349.

Nott, P. N., & Cutts, S. (1982). Validation of the 30-item General Health Questionnaire in postpartum women. *Psychological Medicine, 12*, 409-413.

Noyola, D. E., Demmler, G. J., Nelson, C. T., Griesser, C., Williamson, W. D., Atkins, J. T., et al. (2001). Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. *The Journal of Pediatrics, 138*(3), 325-331.

O'Brien, S. (2004). Treatment options for heroin and other opioid dependence: A guide for users. In National Drug and Alcohol Research Centre (Ed.). Canberra: Australian Government Department of Health and Ageing.

O'Brien, S., Black, W., Degenhardt, L., Roxburgh, A., Campbell, G., de Graaff, B., et al. (2007). Australian Drug Trends 2006: Findings from the Illicit Drug Reporting System (IDRS): National Drug and Alcohol Research Centre.

Oberklaid, F., Sanson, A., & Prior, M. (1986). The development of Australian normative data for infant temperament. *Australian Paediatric Journal, 22*, 185-187.

Odom, J. V., Bach, M., Barber, C., Brigell, M., Marmor, M. F., Tormene, A. P., et al. (2004). Visual evoked potentials standard (2004). *Documenta Ophthalmologica, 108*(2), 115-123.

Oei, J., & Kei, L. (2007). Management of the newborn infant affected by maternal opiates and other drugs of dependency. [Article]. *Journal of Paediatrics and Child Health, 43*(1/2), 9-18. doi: 10.1111/j.1440-1754.2007.00994.x

Olegard, R., Sabel, K. G., Aronsson, M., Sandin, B., Johansson, P. R., Carlsson, C., et al. (1979). Effects on the child of alcohol abuse during pregnancy: Retrospective and prospective studies. *Acta Paediatrica Scandinavica, 275*(Supplement), 112-121.

Ornoy, A., Segal, J., Bar-Hamburger, R., & Greenbaum, C. (2001). Developmental outcome of school-age children born to mothers with heroin dependency: importance of environmental factors. *Developmental Medicine and Child Neurology, 43*(10), 668-675. doi: doi:10.1017/S0012162201001219

Ossenblok, P., Reits, D., & Spekreijse, H. (1992). Analysis of striate activity underlying the pattern onset EP of children. *Vision Research, 32*(10), 1829-1835.

Ostrea, E. M., Ostrea, A. R., & Simpson, P. M. (1997). Mortality within the first 2 years in infants exposed to cocaine, opiate, or cannabinoid during gestation. *Pediatrics, 100*(1), 79-83.

Pan, B. A., Rowe, M. L., Singer, J. D., & Snow, C. E. (2005). Maternal Correlates of Growth in Toddler Vocabulary Production in Low-Income Families. *Child Development, 76*(4), 763-782.

Patel, V., DeSouza, N., & Rodrigues, M. (2003). Postnatal depression and infant growth and development in low income countries: a cohort study from Goa, India. *Archives of Disease in Childhood, 88*(1), 34-37.

Pearson Education. (2008). Bayley–III Technical Report 2: Factors Contributing to Differences Between Bayley–III and BSID–II Scores Retrieved 5th April, 2011, from http://www.pearsonassessments.com/NR/rdonlyres/85553691-1039-4964-8C1C-6F1E9506BE31/0/BayleyIII_TechRep.pdf

Pechnick, R. N. (1993). Effects of Opioids on the Hypothalamo-Pituitary-Adrenal Axis. *Annual Review of Pharmacology and Toxicology, 33*(1), 353-382. doi: doi:10.1146/annurev.pa.33.040193.002033

Pedlow, R., Sanson, A., Prior, M., & Oberklaid, F. (1993). Stability of maternally reported temperament from infancy to 8 years. *Developmental Psychology, 29*(6), 998-1007. doi: 10.1037/0012-1649.29.6.998

Pepper, C., M., & Henderson, G. H. (1980). Opiates and opioid peptides hyperpolarize locus coeruleus neurons in vitro. *Science, 209*, 394-396.

Persson, R., & Ørbæk, P. (2003). The influence of perseonality traits on neuropsychological test performance and self-reported health and social context in women. *Personality and Individual Differences, 34*, 295-313.

Petterson, S. M., & Albers, A. B. (2001). Effects of Poverty and Maternal Depression on Early Child Development. *Child Development, 72*(6), 1794-1813.

Pinto, F., Onofrj, M., Pola, P., Tempesta, E., & Torrioli, M. G. (1986). Fetal addiction to methadone: Postnatal abstinence syndrome and development of visual evoked potentials. *Drug and Alcohol Dependence, 18*(1), 1-10.

Prior, M., Sanson, A., Smart, D., & Oberklaid, F. (1989). The Australian Temperament Project. In G. A. Kohnstamm, J. E. Bates & M. K. Rothbart (Eds.), *Temperament in childhood* (pp. 537-554). Chichester, UK: Wiley.

Prior, M., Sanson, A., Smart, D., & Oberklaid, F. (2000). Pathways from infancy to adolescence: Australian Temperament Project 1983-2000: Australian Institute of Family Studies.

Pryds, O., Trojaborg, W., Carlsen, J., & Jensen, J. (1989). Determinants of visual evoked potentials in preterm infants. *Early Human Development, 19*, 117-125.

Quinlivan, J. A., & Evans, S. F. (2005). Impact of domestic violence and drug abuse in pregnancy on maternal attachment and infant temperament in teenage mothers in the setting of best clinical practice. *Archives of Women's Mental Health, 8*(3), 191-199.

Ram, B., & Hou, F. (2003). Changes in Family Structure and Child Outcomes: Roles of Economic and Familial Resources. *Policy Studies Journal, 31*(3), 309-330.

Ramer, C., & Lodge, A. (1975). Clinical and developmental characteristics of infants of mothers on methadone maintenance. *Addictive Diseases, 2*(2), 227-234.

Reisinger, M. (1985). Buprenorphine as new treatment for heroin dependence. *Drug and Alcohol Dependence, 16*, 257-262.

Rice, D., & Barone, S. (2000). Critical Periods of Vulnerability for the Developing Nervous System: Evidence from Humans and Animal Models. *Environmental Health Perspectives, 108*, 511-533.

Roberts, A. D., Moore, C. F., DeJesus, O. T., Barnhart, T. E., Larson, J. A., Mukherjee, J., et al. (2004). Prenatal stress, moderate fetal alcohol, and dopamine system function in rhesus monkeys. *Neurotoxicology and Teratology, 26*(2), 169-178. doi: DOI: 10.1016/j.ntt.2003.12.003

Robins, L. N., & Mills, J. L. (1993). Effects of in utero exposure to street drugs. *American Journal of Public Health, 83*(12 supplement), 8-32.

Robinson, S. E. (2000). Effect of Prenatal Opioid Exposure on Cholinergic Development. *Journal of Biomedical Science, 7*(3), 253 - 257.

Robinson, S. E. (2002). Effects of perinatal buprenorphine and methadone exposures on striatal cholinergic ontogeny. *Neurotoxicology and Teratology, 24*, 137-142.

Robinson, S. E., Maher, J. R., Wallace, M. J., & Kunko, P. M. (1997). Perinatal Methadone Exposure Affects Dopamine, Norepinephrine, and Serotonin in the Weanling Rat. *Neurotoxicology and Teratology, 19*(4), 295-303. doi: Doi: 10.1016/s0892-0362(97)00018-4

Rosen, T. S., & Johnson, H. L. (1982). Children of methadone-maintained mothers: follow-up to 18 months of age. *Journal of Pediatrics, 101*(2), 192-196.

Rosen, T. S., & Johnson, H. L. (1985). Long-Term Effects of Prenatal Methadone Maintenance. *NIDA Research Monograph, 59*, 73-83.

Ross, J., Teesson, M., Darke, S., Lynskey, M., Ali, R., Ritter, A., et al. (2005). The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS). *Drug and Alcohol Review, 24*(5), 411-418.

Sadeh, A. (2004). A Brief Screening Questionnaire for Infant Sleep Problems: Validation and Findings for an Internet Sample. *Pediatrics, 113*(6), e570-577. doi: 10.1542/peds.113.6.e570

Salo, S., Kivistö, K., Korja, R., Biringen, Z., Tupola, S., Kahila, H., et al. (2009). Emotional Availability, Parental Self-Efficacy Beliefs, and Child Development in Caregiver-Child Relationships with Buprenorphine-Exposed 3-year-olds *Parenting: Science and Practice, 9* (3), 244 - 259.

Sameroff, A. (1998). Environmental Risk Factors in Infancy. *Pediatrics, 102*(5), e1287-1292. doi:

10.1542/peds.102.5.SE1.1287

Sameroff, A., Seifer, R., Barocas, R., Zax, M., & Greenspan, S. (1987). Intelligence quotient scores

of 4-year-old children: social-environmental risk factors. *Pediatrics, 79*(3), 343-350.

Sanchez, E. S., Bigbee, J. W., Fobbs, W., Robinson, S. E., & Sato-Bigbee, C. (2008). Opioid addiction

and pregnancy: Perinatal exposure to buprenorphine affects myelination in the

developing brain. *Glia, 56*(9), 1017-1027.

Sandtorv, L., Reigstad, H., Bruarøy, S., Elgen, I., & Lægreid, L. M. (2009). Substitution treatment of

drug addicts during pregnancy: consequences for the children? [Har legemiddelassistert

rehabilitering i svangerskapet konsekvenser for barna?]. *Tidsskrift for den Norske

Lægeforening 129*(4), 287-290.

Sanson, A., Prior, M., Garino, E., Oberklaid, F., & Sewell, J. (1987). The structure of infant

temperament: Factor analysis of the revised infant temperament questionnaire. *Infant

Behavior and Development, 10*(1), 97-104.

Sanson, A., Prior, M., & Oberklaid, F. (1985). Normative data on temperament in australian

infants. *Australian Journal of Psychology, 37*(2), 185 - 195.

Sarfi, M., Martinsen, H., Bakstad, B., Røislien, J., & Waal, H. (2009). Patterns in sleep-wakefulness

in three-month old infants exposed to methadone or buprenorphine. *Early Human

Development, 85*(12), 773-778.

Scher, M. S., Richardson, G. A., Robles, N., Geva, D., Goldschmidt, L., Dahl, R. E., et al. (1998).

Effects of prenatal substance exposure: Altered maturation of visual evoked potentials.

Pediatric Neurology, 18, 236-243.

Schindler, S. D., Eder, H., Ortner, R., Rohrmeister, K., Langer, M., & Fischer, G. (2003). Neonatal

outcome following buprenorphine maintenance during conception and throughout

pregnancy. *Addiction, 98*(1), 103-110.

Sears, J. M. (2001). The payment of research subjects: ethical concerns. *Oncology Nursing Forum,

28*(4), 657-663.

Seifer, R., Dickstein, S., Sameroff, A. J., Magee, K. D., & Hayden, L. C. (2001). Infant mental health and variability of parental depression symptoms. *Journal of the Academy of Child and Adolescent Psychiatry, 40*(12), 1375-1382.

Shankaran, S., Lester, B. M., Das, A., Bauer, C. R., Bada, H. S., Lagasse, L., et al. (2007). Impact of maternal substance use during pregnancy on childhood outcome. *Seminars in Fetal and Neonatal Medicine, 12*(2), 143-150.

Simon, E. J. (2005). Opiates: Neurobiology. In J. H. Lowinson, P. Ruiz, R. B. Millman & J. G. Langrod (Eds.), *Substance Abuse: A Comprehensive Textbook* (4th ed.). Philadelphia: Lippincott, Williams and Wilkins.

Skarf, B. (1989). Clinical use of Visual Evoked Potentials. *Ophthalmology Clinics of North America, 2*(3), 499-518.

Skari, H., Skreden, M., Malt, U. F., Dalholt, M., Ostensen, A. B., Egeland, T., et al. (2002). Comparative levels of psychological distress, stress symptoms, depression and anxiety after childbirth - a prospective population-based study of mothers and fathers. *British Journa of Obstetrics and Gynaecology, 109*(10), 1154-1163.

Slomka, J., McCurdy, S., Ratliff, E. A., Timpson, S., & Williams, M. L. (2007). Perceptions of Financial Payment for Research Participation among African-American Drug Users in HIV Studies. *Journal of General Internal Medicine, 22*(10), 1403-1409.

Slutsker, L., Smith, R., Higginson, G., & Fleming, D. (1993). Recognizing Illicit Drug Use by Pregnant Women: Reports From Oregon Birth Attendants. *American Journal of Public Health, 83*(1), 61-64.

Sneader, W. (1998). The discovery of heroin. [Article]. *Lancet, 352*(9141), 1697-1699.

Sobrian, S. K., Robinson, N. L., Burton, L. E., James, H., Stokes, D. L., & Turner, L. M. (1989). Neurobehavioral effects of prenatal exposure to cocaine. *Annals of the New York Academy of Sciences, 562*, 383-386.

Soepatmi, S. (1994). Developmental outcomes of children of mothers dependent on heroin or heroin/methadone during pregnancy. *Acta Paediatrica Supplement, 404*, 36-39.

Sostek, A. M., & Anders, T. F. (1977). Relationships among the Brazelton Neonatal Scale, Bayley Infant Scales, and Early Temperament. [Article]. *Child Development, 48*(1), 320-323. doi: 10.1111/1467-8624.ep10439872

Stefovska, V. G., Uckermann, O., Czuczwar, M., Smitka, M., Czuczwar, P., Kis, J., et al. (2008). Sedative and anticonvulsant drugs suppress postnatal neurogenesis. *Annals of Neurology, 64*(4), 434-445.

Substance Abuse and Mental Health Services Administration. (2010). *Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings* (NSDUH Series H-38A, HHS Publication No. SMA 10-4856Findings). Rockville, MD: Retrieved from http://oas.samhsa.gov.

Tansley, B. W., Fried, P. A., & Mount, H. T. J. (1986). Visual processing in children exposed prenatally to marihuana and nicotine: A preliminary report. *Canadian Journal of Public Health. Revue Canadienne de Sante Publique, 77*(Supplement 1), 72-78.

Taylor, M. J., & McCulloch, D. L. (1992). Visual Evoked Potentials in Infants and Children. *Journal of Clinical Neurophysiology, 9*(3), 357-372.

Teesson, M., Baillie, A., Lynskey, M., Manor, B., & Degenhardt, L. (2006). Substance use, dependence and treatment seeking in the United States and Australia: A cross-national comparison. *Drug and Alcohol Dependence, 81*, 149-155.

Teesson, M., Havard, A., Fairbairn, S., Ross, J., Lynskey, M., & Darke, S. (2005). Depression among entrants to treatment for heroin dependence in the Australian Treatment Outcome Study (ATOS): prevalence, correlates and treatment seeking. *Drug and Alcohol Dependence, 78*(3), 309-315.

Tempel, A., Yang, J., & Basheer, R. (1995). Prenatal morphine exposure differentially alters expression of opioid peptides in striatum of newborns. *Molecular Brain Research, 33*(2), 227-232.

Thernlund, G. M., & Samuelsson, M. A. (1993). Parental social support and child behaviour problems in different populations and socioeconomic groups: a methodological study. *Social Science and Medicine, 36*(3), 353-360.

Thomas, A., & Chess, S. (1977). *Temperament and Development*. New York: Brunner/Mazel.

Tiong, G. K. L., & Olley, J. E. (1988). Effects of exposure in utero to methadone and buprenorphine on enkepahlin levels in the developing rat brain. *Neuroscience Letters, 93*(1), 101-106.

Tong, S., Baghurst, P., & McMichael, A. (2006). Birthweight and cognitive development during childhood. *Journal of Paediatrics and Child Health, 42*(3), 98-103.

Totsika, V., & Sylva, K. (2004). The Home Observation forMeasurement of the Environment Revisited. *Child and Adolescent Mental Health, 9*(1), 25–35.

Trimble, M. R. (1990). Antiepileptic Drugs, Cognitive Function, and Behavior in Children: Evidence from Recent Studies. *Epilepsia, 31*, S30-S34. doi: 10.1111/j.1528-1157.1990.tb05867.x

Unden, A. L., & Orth-Gomer, K. (1989). Development of a social support instrument for use in population surveys. *Social Science and Medicine, 29*(12), 1387-1392.

Uysal, S., Renda, Y., Topcu, M., Erdem, G., & Karacan, R. (1993). Evoked potentials in full-term and premature infants: a comparative study. *Child's Nervous System, 9*, 88-92.

van Baar, A. (1990). Development of Infants of Drug Dependent Mothers. *Journal of Child Psychology and Psychiatry, 31*(6), 911-920. doi: 10.1111/j.1469-7610.1990.tb00833.x

van Baar, A., & de Graaff, B. M. T. (1994). Cognitive development at preschool-age of infants of drug-dependent mothers. *Developmental Medicine and Child Neurology, 36*(12), 1063-1075. doi: 10.1111/j.1469-8749.1994.tb11809.x

van Baar, A., Fleury, P., Soepatmi, S., Ultee, C., & Wesselman, P. (1989). Neonatal behaviour after drug dependent pregnancy. *Archives of Disease in Childhood, 64*, 235-240.

van Baar, A., Fleury, P., & Ultee, C. (1989). Behaviour in first year after drug dependent pregnancy. *Archives of Disease in Childhood, 64*(2), 241-245.

van Baar, A., Soepatmi, S., Gunning, W., & Akkerhuis, G. (1994). Development after prenatal exposure to cocaine, heroin and methadone. *Acta Paediatrica. Supplement, 404*, 40-46.

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Vega, W. A., Aguilar-Gaxiola, S., Andrade, L., Bijl, R., Borges, G., Caraveo-Anduaga, J. J., et al. (2002). Prevalence and age of onset for drug use in seven international sites: results from the international consortium of psychiatric epidemiology. *Drug and Alcohol Dependence, 68*(3), 285-297. doi: Doi: 10.1016/s0376-8716(02)00224-7

Verster, A., & Buning, E. (2005). *Buprenorphine: Critical questions examined*. Amsterdam: Quest for Quality BV, Euro-Methwork.

Vicky, R. (2009). Mixed Between-Within Subjects ANOVA. . Retrieved from http://allnurses.com/showthread.php?t=379173

Viggedal, G., Hagberg, B. S., Laegreid, L., & Aronsson, M. (1993). Mental Development in Late Infancy after Prenatal Exposure to Benzodiazepines—a Prospective Study. *Journal of Child Psychology and Psychiatry, 34*(3), 295-305. doi: 10.1111/j.1469-7610.1993.tb00993.x

Watson, E., & Evans, S. J. W. (1986). An example of cross-cultural measurement of psychological symptoms in post-partum mothers. *Social Science and Medicine, 23*(9), 869-874.

Webb, K., Marks, G. C., Lund-Adams, M., Rutishauser, I. H., & Abraham, B. (2001). Towards a national system for monitoring breastfeeding in Australia: recommendations for population indicators, definitions and next steps. Canberra: Commonwealth Department of Health and Aged Care.

Weiss, S. J., Jonn-Seed, M. S., & Harris-Muchell, C. (2007). The contribution of fetal drug exposure to temperament: potential teratogenic effects on neuropsychiatric risk. *Journal of Child Psychology and Psychiatry, 48*(8), 773-784.

Whiffen, V. E., & Gotlib, I. H. (1989). Infants of Postpartum Depressed Mothers: Temperament and Cognitive Status. *Journal of Abnormal Psychology, 98*(3), 274-279.

Williams, P., Piamjariyakul, U., Williams, A., Hornboonherm, P., Meena, P., Channukool, N., et al. (2003). Thai mothers and children and the home observation for measurement of the environment (home inventory): pilot study. *International Journal of Nursing Studies, 40*(3), 249-258.

Wilson, G. S. (1989). Clinical studies of infants and children exposed prenatally to heroin. *Annals of the New York Academy of Sciences, 562*, 183-194.

Wilson, G. S., Desmond, M. M., & Verniaud, W. M. (1973). Early development of infants of heroin-addicted mothers. *American Journal of Diseases of Children, 126*, 457-462.

Wilson, G. S., Desmond, M. M., & Wait, R. B. (1981). Follow-up of methadone-treated and untreated narcotic-dependent women and their infants: Health, developmental, and social implications. *The Journal of Pediatrics, 98*(5), 716-722. doi: Doi: 10.1016/s0022-3476(81)80830-x

Wilson, G. S., McCreary, R., Kean, J., & Baxter, J. C. (1979). The development of preschool children of heroin-addicted mothers: A controlled study. *Pediatrics, 63*(1), 135-141.

Wu, V. W., Mo, Q., Yabe, T., Schwartz, J. P., & Robinson, S. E. (2001). Perinatal opioids reduce striatal nerve growth factor content in rat striatum. *European Journal of Pharmacology, 414*, 211-214.

Zacny, J. P., & Walker, E. A. (1998). Behavioral Pharmacology of Opiates. In R. E. Tarter, R. T. Ammerman & P. J. Ott (Eds.), *Handbook of substance abuse: neurobehavioral pharmacology* (pp. 343-363). New York: Plenum Press.