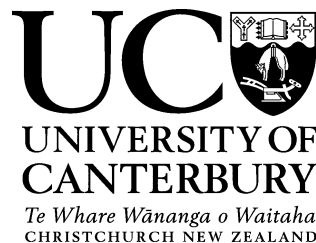

Educational Outcomes at Age 9 Years of Children Prenatally Exposed to Methadone

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A thesis submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in Psychology



UNIVERSITY OF CANTERBURY

2018

DEDICATION

This thesis is dedicated to Alison Jean Lee (Gran).



Gran was a pillar of strength throughout the PhD process, providing consistent emotional support with her gentle, encouraging words. She was never granted, and always wished for, the opportunity to attain secondary and tertiary education. She always assured me that I would never regret furthering my education. I know she is as proud of me for completing this degree as I am grateful to her for reminding me how fortunate I have been in choosing to study.

ACKNOWLEDGEMENTS

In completing this thesis I was lucky enough to have been helped, supported and encouraged by numerous people. Without such a network of special individuals, my doctoral research would not have been successful. Although there are many to thank, I wish to acknowledge those that have had a particular influence along my journey.

First, I wish to thank Dr Jacki Henderson, my primary thesis supervisor, for her academic and emotional support throughout my PhD candidature. I am grateful to Jacki for always driving me to produce high quality work and, in turn, for immensely improving my academic skills. I am appreciative of Jacki's willingness to quell any of my concerns, whether at times of convenience at the office or, less conveniently, at her children's tennis matches. Finally, I am thankful for all of the career-building opportunities Jacki has offered me. Along with the chance to work on a world-first study, Jacki assisted with scholarship applications, conference attendance, and teaching opportunities.

Thanks are also due to my other thesis supervisors for their time and mentorship. Janet: thank you for your invaluable feedback and advice. Katharina: I appreciated your friendly approach and statistical support. Lianne: your guidance has been cherished over the years that I have been working on the Methadone in Pregnancy Study. I am always grateful for the experience that I have gained as a member of this high quality research program.

A special thank you is also owed to other members of the Canterbury Child Development Research Group. Karella Levin, Melissa Laird, Marie Goulden, Alison Davie-Gray, Jamie Stringer, Sophia Bennetts and Emma Jordan: thank you for your help with family recruitment and data collection for this study, for providing a source of unwavering friendship, and for always lending an ear. Thanks also go to Nicola Austin for offering her medical expertise, and to Carole Spencer, Trish Graham and Nicola Ellis for assisting with the successful retention of our study families for over 9 years. Thank you also to Sam Bora for his mentorship. Finally, thanks to Julie Cox for providing support, amidst lots of laughs, in the office.

I would also like to acknowledge the New Zealand Lottery Grants Board for awarding me a generous PhD scholarship which allowed me to devote my time to this research. Thank you to the Graduate Women Canterbury Trust for their financial support to present my research findings overseas.

More personally, I wish to express how lucky I have been to have my family and friends supporting me throughout my university ventures. In particular, thank you Robbie for your encouragement and patience, as well as your ability to mix good humour with a few stern words when we both knew it was time to keep it real. Mum and Dad: I have become more and more thankful to you as I wrote this thesis about children's education and learning opportunities. Thank you for always backing me no matter what I studied, or for how long. I would also like to acknowledge Dr Raeburn Lange who, in the final moments, proofread this thesis at the speed of light.

Finally, thank you to all of the amazing study children, families and whānau for taking part in this research. I will always treasure the opportunity I have had to learn about the children's development over the 6 years that I worked on this longitudinal study. This experience has greatly influenced my life, and will never be forgotten.

ABSTRACT

The prevalence of opioid use among pregnant women is an increasing global health concern. Methadone maintenance therapy is associated with improved health outcomes for opioid-dependent pregnant women and their infants compared with ongoing illicit opioid abuse. Infants who have been prenatally exposed to methadone are reported to have high rates of neonatal abstinence syndrome, and show neurodevelopmental difficulties to age 4 years. There are no studies of methadone-exposed children to middle childhood (6 to 12 years) to date. Of critical concern, middle childhood educational outcomes are key for lifelong psychosocial success. Further, the extent to which prenatal methadone exposure and other related prenatal and postnatal risks contribute to children's educational skill development remains unknown.

This thesis had three aims: 1) to describe the educational outcomes of a New Zealand cohort of 9-year-old methadone-exposed children compared to non-methadone-exposed children. Educational outcomes included children's performance on standardised reading and mathematics tests, their teacher-rated school performance, and special education enrolment; 2) to assess the extent to which between-group differences in children's educational outcomes reflect the direct effects of prenatal methadone exposure when adjusting for confounding factors spanning maternal social background, other prenatal drug exposures, and infant medical factors; and 3) to investigate whether between-group differences in children's caregiving factors exist from birth to age 9 years and whether caregiving differences, in turn, predict poorer educational outcomes for methadone-exposed children.

There were 62 methadone-exposed and 72 non-methadone-exposed children who were assessed at age 9 years in a prospective longitudinal study. Educational outcomes were assessed using the Woodcock Johnson-III Tests of Achievement (Woodcock, McGrew, & Mather, 2001) during a comprehensive neurodevelopmental assessment, and children's primary class teacher completed a questionnaire about their school achievement. Potential maternal and infant confounding factors were measured at term, and caregiving data were collected at 2, 4.5 and 9 years.

Methadone-exposed children had poorer educational outcomes compared to non-methadone-exposed children. Specifically, their risk for having a reading and/or a mathematics delay was 4.5 times greater (57% vs. 13%, $OR = 9.1 [3.8 - 21.5]$), they were underachieving across subjects of the New Zealand curriculum (26% to 65% vs. 8 to 22%),

and a higher proportion were enrolled in special education (37% vs. 10%). Methadone-exposure remained associated with educational delay ($p = .02$) following adjustment for a wide range of term confounding factors. However, there were between-group differences in caregiving factors which, in turn, were shown to predict poorer 9-year educational outcomes for methadone-exposed children. The specific intervening factors were a higher number of primary caregiver changes from birth up to 9 years, and higher caregiver depression scores at 18 months ($ps < .05$). Methadone-exposed children also had lower school readiness at age 4.5 years which, in turn, predicted 9-year educational delay ($p < .05$).

At 9 years, children exposed prenatally to methadone were at increased risk for adverse educational outcomes characterised by poor reading, mathematics, and overall academic achievement compared to their non-methadone-exposed peers. Their increased educational risk could not be fully explained by confounding maternal or infant factors. Postnatal caregiving risks were key predictors for these children's educational outcome, emphasising the importance of routine educational assessment for this high-risk group. In addition, findings suggest that multi-disciplinary intervention services to school age will be necessary to remediate some of the educational risk for methadone-exposed children.

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LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
CCDRG	Canterbury Child Development Research Group
CELF-P	Clinical Evaluation of Language Fundamentals – Preschool
CNS	Central nervous system
EPDS	Edinburgh Postnatal Depression Scale
HIV	The human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal (axis)
HOME	Home Observation for Measurement of the Environment
MDI	Mental Developmental Index
ME	Methadone-exposed
MIP	Methadone in Pregnancy
MMT	Methadone maintenance therapy
MRI	Magnetic resonance imaging
NAS	Neonatal abstinence syndrome
OE	Opioid-exposed
OR	Odds ratio
ORS	Ongoing Resourcing Scheme
OST	Opioid substitution treatment
PKRS-II	Phelps Kindergarten Readiness Scale – II
RTLb	Resource Teachers of Learning and Behaviour
SDQ	Strengths and Difficulties Questionnaire
SES	Socioeconomic status
VMI	Visual Motor Integration
WASI-II	Wechsler Abbreviated Scale of Intelligence – second edition
WJ-III	Woodcock-Johnson III Tests of Achievement
WPPSI-R	Wechsler Preschool and Primary Scales of Intelligence – revised

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PREFACE

Author's Contribution

The author of this thesis was a member of the 9-year follow-up of the Canterbury Methadone in Pregnancy Study. She was responsible for:

- Inviting families to participate and informing them on the 9-year study procedures
- Providing transport assistance to study families who needed it
- Preparation of the research facility and the assessment tasks
- Assisting with the administration of several cognitive and behavioural tasks. The Wechsler Abbreviated Scale of Intelligence, Woodcock-Johnson III Tests of Achievement, and Clinical Evaluation of Language Fundamentals were administered under clinical supervision. A number of experimental self-regulation measures were also administered.
- Administration and collection of the teacher questionnaire
- Data entry, cleaning, analysis, and interpretation

Introduction Overview

The introduction section of this thesis is organised into five chapters.

Chapter 1: Provides an overview of opioid dependence and methadone maintenance treatment for opioid dependence during pregnancy. The potential effects of prenatal methadone exposure on foetal development and neonatal outcomes are described.

Chapter 2: Reviews the literature describing the neurodevelopmental outcomes of children born to opioid-dependent mothers. Limitations of the extant research are discussed.

Chapter 3: Describes typical educational achievement to age 9 years, the target age group of this thesis. Educational delay is defined.

Chapter 4: Reviews the literature examining the educational outcomes of school-age children born to opioid-dependent mothers.

Chapter 5: Discusses the socio-environmental risk factors, i.e. caregiving factors, which may increase the risk for poor educational outcomes among prenatally methadone-exposed children.

CHAPTER 1

Opioid Dependence during Pregnancy and Methadone Maintenance Treatment

Prescription and illicit opioid abuse is an increasing worldwide health concern. Prevalence rates of those with an opioid dependence range between 0.5% to 1% (Ministry of Health, 2014; United Nations Office on Drugs and Crime, 2016), and women of child-bearing age are amongst those with this complex and debilitating mental health condition (Cicero, Ellis, Surratt, & Kurtz, 2014; Patrick et al., 2012). Maternal opioid dependence has important adverse implications for child welfare, health and development (Solis, Shadur, Burns, & Hussong, 2012). In light of the recent increases in opioid dependence, systematic and rigorous empirical investigations of the effects of prenatal opioid exposure on children's neurodevelopmental outcomes is warranted.

To date, no empirical investigations have described the educational outcomes of 9-year-old children who were born to opioid-dependent mothers treated with methadone during pregnancy. This is the overarching aim of the current thesis. Educational achievement during middle childhood (age 6 to 12 years) has important lifelong psychosocial and occupational consequences, and therefore research examining the educational outcomes of prenatally methadone-exposed children is clearly necessary. The first chapter provides an overview of opioid dependence and its treatment, followed by a description of the prenatal risks associated with maternal opioid dependence during pregnancy.

1.1 Opioid Dependence

Opioids are narcotic substances derived from the opium poppy. They include opium, heroin, analgesic medications (e.g. morphine, codeine, and oxycodone) and synthetic opioids

that are used in the treatment of opioid dependence (e.g. methadone and buprenorphine). The addictive properties of opioids are due to their actions at the opioid receptors in the central nervous system (CNS; Pasternak, 2011). Opioid substances mimic the actions of endogenous opioid neuropeptides by binding to delta, kappa, and mu opiate receptors and activating their antinociceptive or pain-modulation systems (Al-Hasani & Bruchas, 2011; Stoelting & Miller, 2007). This activation occurs through inhibiting the release of neurotransmitters into the synaptic cleft which, in addition to analgesia, produces respiratory, cardiovascular and gastrointestinal depression. It also produces sedation and euphoria which are psychologically reinforcing (Chahl, 1996; Reisine & Bell, 1993).

The chronic, compulsive misuse of opioid substances over time leads to the development of physical dependence which results in withdrawal symptoms upon discontinued opioid use. These adverse symptoms, including nausea, palpitations, anxiety and drug cravings (bpac^{nz}, 2014; National Association of Opioid Treatment Providers, 2010), make attempts to abstain from use difficult and frequently unsuccessful. Thus, opioid dependence is characterised by a debilitating cycle of opioid abuse, withdrawal and relapse (Peachey & Lei, 1988; Swift & Stout, 1992). Over time, chronic users will also experience tolerance to the effects of opioid substances and will need to consume increasing amounts to experience the desired analgesic and euphoric effects (Bailey & Connor, 2005).

Opioid dependence is associated with both social and health-related harm. The time that opioid-dependent individuals spend engaging in obtaining, using and recovering from the intoxicating effects of opioids impacts relationships and work commitments, and is proportionately associated with an increase in criminal activity (Wilkins, Prasad, Wong, & Rychert, 2013). Substance abusers' preoccupation with drug-seeking and administration may compromise proper nutrition and personal care, thereby adversely affecting general health (United Nations Office on Drugs and Crime, 2016). A major health risk to opioid-dependent

individuals is the transmission of blood-borne viruses, such as the human immunodeficiency virus (HIV) and hepatitis, through needle-sharing (Bruneau, Roy, Arruda, Zang, & Jutras-Aswad, 2012; MacArthur et al., 2012). Risk of death is also a major concern. An estimated 1% of adult deaths worldwide are attributable to illicit substance use, predominantly from overdose (United Nations Office on Drugs and Crime, 2016). Treating individuals with opioid dependence is clearly crucial for reducing the associated harm.

1.2 Opioid Substitution Treatment for Opioid Dependence in New Zealand

Approximately 10,000 New Zealand (NZ) adults use opioids daily (Adamson et al., 2012; Deering, Sellman, & Adamson, 2014). Internationally, heroin is a commonly misused opioid. Opioid-dependent adults in NZ, however, primarily use home-produced injectable substances derived from morphine and other opioid-based pharmaceuticals (Harris, 2013; National Association of Opioid Treatment Providers, 2010; Wilkins et al., 2013). The recent increase in opioid prescribing has also contributed to the elevated rates of opioid dependence in this country. In alignment with international trends the number of NZ patients prescribed oxycodone relates directly to the increased problematic misuse of this substance (bpac^{NZ}, 2012, 2014; Ministry of Health, 2010). Data from a recent NZ drug trends survey showed a more than 45% increase in oxycodone abuse among frequent injecting drug users from 2008 to 2013 (Wilkins et al., 2013).

Opioid substitution treatment (OST) is the primary treatment option for reducing the health and social harms attributable to opioid dependence (Deering et al., 2014; Murphy & Polsky, 2016; Sheerin, Green, Sellman, Adamson, & Deering, 2004). Approximately 50% of the estimated daily opioid users in NZ are currently enrolled in OST services. Opioid substitution treatment involves a comprehensive assessment of individual treatment needs by combining specialist psychosocial support with a prescribed opioid substitute (Adamson et

al., 2012; Deering et al., 2014; Ministry of Health, 2014). Two of the most commonly prescribed opioid substitutes for the treatment of opioid dependence worldwide are methadone and buprenorphine. Methadone is currently the gold-standard treatment for opioid dependence in NZ, but buprenorphine prescribing is beginning to emerge.

Methadone has been used in the treatment of opioid dependence since the 1960s. It was first discovered as a treatment by Vincent Dole and Marie Nyswander (Dole & Nyswander, 1965) who used the drug to successfully treat male heroin-addicted patients in the United States (US). Compared to other experimental treatments such as long-acting morphine, methadone was observed to successfully lower patients' opioid cravings for an extended duration, with subsequent improvements in work and social functioning. Research has since shown that opioid-dependent individuals treated with methadone have increased employment opportunities, and show more prosocial behaviour and reduced substance-related criminal activity than illicit opioid addicts (Gossop, Marsden, Stewart, & Treacy, 2001). Furthermore, because of reduced intravenous drug use and needle-sharing there is a decreased prevalence of HIV and hepatitis amongst patients enrolled in methadone maintenance treatment (MMT) compared with illicit opioid users (Ball, Lange, Myers, & Friedman, 1988; MacArthur et al., 2012).

The relative behavioural stability observed following methadone administration is due to the drug's pharmacokinetic properties. Methadone is a full opioid agonist that binds specifically to mu-opiate receptors in the CNS (Garrido & Trocóniz, 1999). It is rapidly absorbed into the blood plasma following its oral administration where it occupies these receptors and blocks the reinforcing effects of any other consumed opioids. Methadone is also readily distributed among body tissues including the brain, liver and gut. As blood plasma concentrations begin to metabolise and decrease over time methadone is reabsorbed from these body tissues and continues to occupy the critical receptors (Dole, 1988). This

reverse absorption process gives methadone its long-lasting action, delaying withdrawal symptoms until around 24 to 36 hours following administration. This makes it possible for most patients to function without physiological or behavioural disturbance when maintained on one daily therapeutic dose (Dole & Kreek, 1973; Eap, Buclin, & Baumann, 2002).

1.3 Methadone Maintenance Treatment for Opioid Dependence during Pregnancy

1.3.1 Prevalence of opioid dependence during pregnancy. Opioid use and dependence among pregnant women is an international concern. The worldwide prevalence of maternal opioid dependence in pregnant women is estimated at between 1% and 2%, increasing to 21% in some areas (Minozzi, Amato, Bellisario, Ferri, & Davoli, 2013). In the US there was a 127% increase in opioid dependence among pregnant women, from 1.7 per 1,000 delivery admissions in 1998, to 3.9 per 1,000 in 2011 (Maeda, Bateman, Clancy, Creanga, & Leffert, 2014; Salihu, Mogos, Salinas-Miranda, Salemi, & Whiteman, 2015). Exact prevalence rates of opioid use or dependence during pregnancy in NZ are currently unavailable. However the majority of NZ women that use opioids are reported to be of childbearing age (Ministry of Health, 2010; Wilkins et al., 2013).

Concernedly, opioid-dependent women have higher pregnancy rates than the general adult female population, and their pregnancies are more likely to be complicated by a number of adverse obstetric outcomes requiring medical intervention (Black, Stephens, Haber, & Lintzeris, 2012). Outcomes associated with prenatal opioid abuse include miscarriage, placental abruption, preterm birth, stillbirth, cardiac problems and maternal death; complications that come at a large cost, both in terms of maternal and infant well-being and in health service provision (Lam, To, Duthie, & Ma, 1992; Ludlow, Evans, & Hulse, 2004; Maeda et al., 2014; Patrick et al., 2012). In a recent study Whiteman et al. (2014) found that

delivery hospitalisation for pregnant opioid users in the US was over \$2600 more per discharge than for non-users, approximating \$30 million per year.

1.3.2 Harm reduction by MMT during pregnancy. Opioid-dependent pregnant women are encouraged to enrol in OST to reduce the obstetric risks associated with illicit opioid dependence. Methadone maintenance treatment is currently the primary OST option recommended for opioid-dependent mothers in NZ (Matua Raki, 2015; Ministry of Health, 2014). In NZ, MMT during pregnancy includes a daily methadone prescription alongside access to specialised antenatal care where maternal and foetal health are closely monitored by health-care professionals (Community Alcohol and Drug Services, 2011; Ministry of Health, 2014). Methadone maintenance helps minimise the fluctuating cycle of foetal opioid intoxication and withdrawal associated with illicit opioid abuse, helping to promote longer gestation and healthier foetal growth (Bonello et al., 2014; Chasnoff, Burns, Burns, & Schnoll, 1985; Hulse, Milne, English, & Holman, 1997; Kandall, Doberczak, Jantunen, & Stein, 1999; Ornoy, Michailevskaya, Lukashov, Bar-Hamburger, & Harel, 1996). Further, as MMT enrolment reduces risky maternal behaviours such as needle-use, there is also a lower likelihood that the mother will contract and transfer a blood-borne infection to her developing foetus (Naeye, Blanc, Leblanc, & Khatamee, 1973; Wagner, Katikaneni, Cox, & Ryan, 1998; Whiteman et al., 2014).

1.4 Foetal and Neonatal Outcomes of Prenatal Methadone Exposure

Methadone is a lipophilic compound with a low molecular weight that readily crosses the placenta (Nekhayeva et al., 2005). The foetal and neonatal outcomes, including the growth, health and delivery outcomes, of infants born to mothers in MMT are clearly favourable compared to infants born to untreated opioid-dependent women. However maternal enrolment in MMT during pregnancy does not appear to be completely risk free,

and has been associated with a number of adverse foetal and neonatal outcomes when compared to non-methadone-exposed pregnancies. Research studies have shown a strong relationship between prenatal methadone exposure and altered foetal breathing and body movements (McCarthy, Leamon, Finnegan, & Fassbender, 2016; Richardson, O'Grady, & Olsen, 1984; Wittmann & Segal, 1991; Wouldes, Roberts, Pryor, Bagnall, & Gunn, 2004). For example, using prenatal ultrasound technology, a suppression of both total foetal breathing movements and breathing rate measured 1- and 2-hours following maternal methadone consumption, was reported (Richardson et al., 1984; Wittmann & Segal, 1991; Wouldes et al., 2004). Increased foetal body movements prior to daily maternal methadone consumption was found in some studies, signifying motor hyperactivity that is suggested to be caused by foetal opioid withdrawal (McCarthy et al., 2016; Richardson et al., 1984; Wittmann & Segal, 1991).

Prenatal methadone exposure is also associated with prematurity and intrauterine growth restriction. Prevalence rates of preterm birth vary across studies, with between 5% to > 50% of methadone-exposed (ME) infants born before 37 weeks gestation (Bakstad, Sarfi, Welle-Strand, & Ravndal, 2009; Bier, Finger, Bier, Johnson, & Coyle, 2015; Brogly et al., 2017; Cleary et al., 2012; Gray et al., 2010; Wouldes & Woodward, 2010). Many full-term born ME infants are observed to have a lower birth weight, birth length, and head circumference than non-ME infants (Hulse et al., 1997; Kaltenbach & Finnegan, 1984; Konijnenberg, Sarfi, & Melinder, 2016; McGlone & Mactier, 2015; Pinto et al., 2010; Walhovd, Watts, Amlien, & Woodward, 2012; Wouldes & Woodward, 2010).

Neonatal abstinence syndrome (NAS) is one of the most clinically significant outcomes associated with prenatal methadone exposure. Neonatal abstinence syndrome is an opioid withdrawal syndrome characterised by CNS irritability, autonomic over-reactivity, gastrointestinal dysfunction, and respiratory distress (Cleary et al., 2010; Greig, Ash, &

Douiri, 2012; Huestis & Choo, 2002). The symptoms can include tremors, hypertonicity, excessive and high-pitched crying, sweating, yawning, sneezing, difficulty feeding, diarrhoea, nasal stuffiness, rapid breathing, and temperature instability. Seizures may also be present in severe cases (Gaalema et al., 2012; Hudak et al., 2012; Jones & Fielder, 2015; Ko, 2016; Kocherlakota, 2014; Quick, Robb, & Woodward, 2009).

Up to 90% of infants exposed to opioids *in utero* experience NAS (Cleary et al., 2010; Greig et al., 2012; Huestis & Choo, 2002). Infants with NAS require tapering doses of an opioid such as morphine or methadone to manage their withdrawal symptoms. The symptoms are usually observed in ME infants by 48 to 72 hours after birth, and the duration and severity of the symptoms varies across infants (Jansson & Velez, 2016). There is no conclusive evidence suggesting a relationship between maternal methadone dose during pregnancy and infant NAS severity or duration. In a systematic review, Cleary et al. (2010) found a relationship between maternal methadone dose and NAS incidence, severity and duration across 19 studies, and no relationship across the same number of studies. Divergent findings continue to be reported in more recent literature, with some investigators reporting no effect of dose on NAS outcomes (Gray et al., 2010; Jones, Jansson, O'Grady, & Kaltenbach, 2013), and others reporting a dose-response relationship (Bier et al., 2015; Wouldes & Woodward, 2010).

1.5 Prenatal Action Mechanisms of Methadone on the Developing Foetus

Numerous mechanisms of influence are implicated in the prenatal development of ME children. These include the direct neurochemical effects of methadone itself, and a number of potentially confounding influences. A confounder is an extraneous factor associated with both the exposure and the outcome of interest. Without appropriate control for extraneous factors, it is possible that confounding effects on the outcome could become mixed with the

effect of interest (Boslaugh, 2008). Potential confounders of prenatal methadone exposure could include: (a) indirect effects on the developing foetus through the effects of methadone and associated lifestyle factors on the mother, (b) additional prenatal drug exposures, and (c) epigenetics or biological “programming” and genetic effects. Each of these potential mechanisms of action is further described below.

1.5.1 Direct neurochemical effects of prenatal methadone exposure. Prenatal exposure to methadone may directly affect the structure and function of the developing foetal brain by impacting normal neuronal organisation, and causing alterations in neurotransmitter and receptor development (Behnke, Smith, & Committee on Substance Abuse, 2013; Farid, Dunlop, Tait, & Hulse, 2008). Findings from existing experimental research suggest that prenatal methadone exposure is associated with neuron loss and abnormal neural proliferation (Farid et al., 2008). Accelerated oligodendrocyte cell maturation and myelin development has been reported following perinatal methadone exposure in the developing rat pup brain, suggestive of a disruption in normal neural connectivity (Vestal-Laborde, Eschenroeder, Bigbee, Robinson, & Sato-Bigbee, 2014). Other rat studies have shown decreased cerebral weights and a reduction in neuronal cells following prenatal exposure (Ford & Rhines, 1979; Zagon & McLaughlin, 1982). Similarly, methadone injected into chick embryos was reported to decrease the average number of neurons in the chick equivalent of the prefrontal cortex, suggesting an adverse effect of methadone on the production, growth and migration of neurons (Gagnon, Dingman, D’Arco, & McGinnis, 2015).

Studies examining human brain development have also shown that prenatal methadone exposure may affect infant brain growth and neural transmission. In a neonatal magnetic resonance imaging (MRI) study using volumetric methods, Yuan et al. (2014) found that infants born to mothers using opioids during pregnancy had smaller whole brain volumes compared to general population means. Sirnes et al. (2017) found significantly

smaller volumes of the basal ganglia, thalamus, and cerebral white matter of children with prenatal heroin or methadone exposure compared with age- and sex-matched controls aged 10 to 14 years. In a study that used diffusion tensor imaging, Walhovd et al. (2012) found higher mean diffusivity in ME infant's brain tracts relative to non-ME infants at term. Higher mean diffusivity of the connective tracts reflected less mature, or developmentally altered neural connective tracts, as well as alterations in the ME infant's neural myelination. Given the role of myelin in efficient nerve impulse conduction, this may be associated with negative long-term cognitive consequences (Walhovd et al., 2012). In another recent diffusion MRI study, Monnelly et al. (2018) found an independent association between prenatal methadone exposure and altered microstructure in white matter tracts of the newborn brain, suggesting lower fibre density, axonal growth, and myelination compared to non-exposed controls.

The structural brain morphology of children born to opioid-dependent mothers in these studies may be at risk due to adverse effects of prenatal opioids on the developing brain. Maternal opioid-dependence is, however, also associated with several other risk factors that may compromise foetal and later child development. Importantly, drawing conclusions about methadone's teratogenic impacts cannot be made without considering the possible confounding effects of poly-drug use, maternal lifestyle factors, and genetics, as briefly described below.

1.5.2 Indirect effects of prenatal maternal methadone maintenance. Maternal methadone maintenance during pregnancy is related to increased obstetric complications, preterm birth, and foetal growth restriction. These adverse neonatal outcomes may be related to the pharmacological effects of methadone on the mother, which then may indirectly impact the developing foetus. Methadone may cause placental insufficiency as well as placental and umbilical blood vessel constriction, essentially limiting foetal blood supply and altering substrate delivery to the foetus. Decreased placental blood flow may cause foetal

undernourishment or hypoxia, potentially compromising *in utero* development (Behnke et al., 2013; Farid et al., 2008; Lester & Padbury, 2009).

Maternal health and behaviours attributable to opioid dependence, including poor maternal nutritional intake, infections such as hepatitis, a stressful and chaotic lifestyle, and poor psychological well-being, may also place the foetus at risk for prematurity or growth restriction (Bauer et al., 2002; Behnke et al., 2013; Lifschitz, Wilson, Smith, & Desmond, 1983; Moody, Chen, & Pan, 2017). This is concerning given the negative impact of preterm birth and/or low birth weight on negative longer-term neurodevelopmental outcomes, including higher rates of cognitive delay and learning difficulties during the school years (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Jaekel & Wolke, 2014; Pritchard et al., 2009).

1.5.3 Other prenatal drug exposures. Women receiving MMT are likely to use a number of licit and illicit psychoactive substances during pregnancy, despite being in treatment for opioid dependence (Bernstein & Hans, 1994; Davie-Gray, Moor, Spencer, & Woodward, 2013). Prenatal tobacco, alcohol, cannabis, cocaine, and other illicit substance exposures are independently associated with an increased risk of preterm birth and intrauterine growth restriction compared with no substance use during pregnancy, and are also associated with later emotional, behavioural, language, and educational problems (e.g. Behnke et al., 2013; Conradt et al., 2014). It has also been hypothesised that the greater the number of different substances a child is prenatally exposed to, the greater the amount of stress and harm experienced by the foetus during development (Bada et al., 2012; Conradt et al., 2014). Maternal poly-drug use, particularly concomitant cigarette use, may be associated with increased postnatal neurobehavioural dysregulation among ME infants, as indicated by more severe and prolonged NAS (Bakstad et al., 2009; Jansson, Velez, & Harrow, 2009). It

is currently unknown whether prenatal poly-drug exposure will negatively impact on ME infant's longer-term outcomes to middle childhood.

1.5.4 Biological “programming” and genetics. Intrauterine stress caused individually or cumulatively by methadone and poly-drug exposure, maternal infection, and/or maternal stress may indirectly impact ME children's longer term development through foetal programming (Glover, O'Connor, & O'Donnell, 2010). Lester and Padbury (2009) described how an intrauterine stressor such as prenatal drug exposure can disrupt foetal development by altering the expression of key genes and causing structural and functional brain changes. These epigenetic alterations are thought to occur in response to direct environmental stress in order to better prepare the foetus for optimal postnatal environmental adaptation. However in the case of prenatal drug abuse, these foetal responses may serve no postnatal purpose and may have long-term maladaptive effects on children's neurodevelopmental outcomes (Lester & Lagasse, 2010; Lester & Padbury, 2009).

Methadone-exposed infants might also undergo permanent physiological alterations following opioid withdrawal. For example, the underlying stress of prenatal withdrawal or NAS may be associated with neurodevelopmental and functional changes to the hypothalamic-pituitary-adrenal (HPA) axis (Dutriez-Casteloot et al., 1999; Hambleton et al., 2013; Konijnenberg, Lund, & Melinder, 2015; Laborie et al., 2005; Lester & Padbury, 2009). The HPA axis is a neuroendocrine system involved in the production of stress hormones such as cortisol, which is implicated in stress reactivity (Frodl & O'Keane, 2013; Glover et al., 2010). Regulation of the HPA axis may be affected when infants experience extended physiological stress, with potentially adverse consequences for stress reactivity and neurodevelopment, including increased behaviour problems and poor school outcomes (Conradt et al., 2014; Glover et al., 2010; Henry, Kabbaj, Simon, Moal, & Maccari, 1994).

Heritable traits transmitted from opioid-dependent mothers to their children may also place ME children at risk of a poor developmental trajectory. Genetically-conferred characteristics may include lower cognitive ability or increased risk for psychopathology, including a general vulnerability for developing the externalising disorders that may have, in part, contributed to their mothers' trajectory of substance abuse (Bernstein & Hans, 1994; Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Lugoboni et al., 2017; Oliver & Plomin, 2007). A study of opioid-dependent mothers and their school-age children, for example, indicated that attention deficit hyperactivity disorder (ADHD) symptomology was increased among these dyads when compared to non-opioid-dependent mothers and their children (Ornoy, Segal, Bar-Hamburger, & Greenbaum, 2001). Nonetheless, variation in levels of ADHD symptomology was also found within the opioid-exposed group of children. The exposed children raised by their biological mothers showed increased ADHD symptoms than exposed children who were raised by higher SES foster parents, indicating a potential gene-environment interaction for the development of ADHD in their cohort.

1.6 A “Dual Hazard” Model of Development

In addition to the accumulation of intrauterine and early postnatal stressors typically experienced by ME children, many will be exposed to psychosocial adversity and a chaotic caregiving environment. As will be further described in the following chapters, ME children are more likely to be raised in environments that increase their risk for poor development. Maternal opioid dependence generally occurs in the context of multiple social risk factors, including lower educational attainment, greater financial instability, and higher rates of unemployment and single parenthood than non-drug-dependent women. Further, disadvantaged minority populations tend to be overrepresented among methadone-maintained women (Davie-Gray et al., 2013; Hans & Jeremy, 2001; Konijnenberg et al., 2015; McGlone

& Mactier, 2015; Wouldes & Woodward, 2010). Many mothers in MMT also have comorbid mental health problems including depression, anxiety, and personality disorders (Davie-Gray et al., 2013; Oei et al., 2009). Consequentially, ME children are a group at dual hazard for poor developmental outcomes. A major challenge to researchers lies in untangling whether there are independent impacts of prenatal methadone exposure, or whether associated psychosocial and environmental factors have the greatest impact on ME children's later development.

Drawn from Lester and Tronick (1994), Figure 1.1 (page 15) is an illustration of the complex and dynamic relationship between prenatal substance exposure and postnatal environmental influences on a child's later development. Their transactional developmental framework provides a conceptual model for studying the extent to which prenatal methadone exposure affects child development, whilst considering multiple influential social and family factors. Lester and Tronick purport that prenatal drug exposures may have at least a short-term effect on foetal growth and neurobehaviour in the neonatal period. Exposed children's early biological vulnerability may then either be exacerbated or buffered from further risk, depending on the socio-environmental context in which they develop (Bandstra, Morrow, Mansoor, & Accornero, 2010; Johnson, Glassman, Fiks, & Rosen, 1990; Ornoy et al., 2001; Rasmussen, Borelli, Decoste, & Suchman, 2016). However, ME infants often grow up in environments that have a negative effect on their development. A non-supportive caregiving environment makes it that much more difficult for an already stressed infant to recover and thrive.

Lester and Tronick's model also highlights the important transactional role of mutual regulation in the optimal development of substance-exposed children. Specifically, the child's own characteristics, such as temperament and behaviour, and those of their caregivers will continue to mutually influence one another in a bi-directional way. That is, parenting

processes will influence children's behaviour and children's behaviour will influence parenting processes (Beeghly & Tronick, 1994; Belsky & MacKinnon, 1994; Bronfenbrenner & Morris, 1998; Goodman, Hans, & Bernstein, 2005; Ryan & Adams, 1995; Sameroff, 1975). The wider environmental context (commonly characterised by poverty and comorbid mental health problems) in which these interactions take place has the potential to impinge on the mother-infant interactions and the mutual regulatory process, with negative outcomes for infant development. A major interest in this thesis thus concerns how postnatal factors are implicated in the transmission of risk to ME children. The theory currently suggests that any longer term effects of methadone will be mediated by environmental factors.

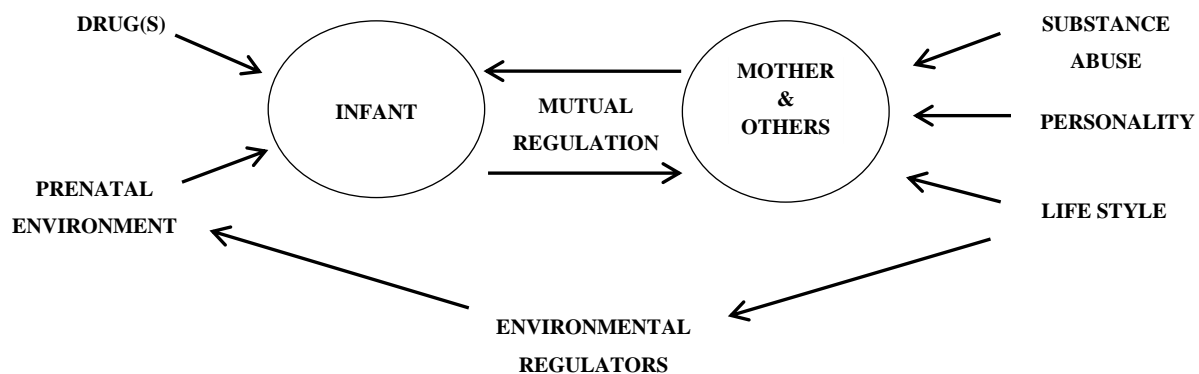


Figure 1.1. Systems approach to the study of cocaine (Lester & Tronick, 1994).

1.7 Chapter Summary

Opioid dependence during pregnancy is an increasing problem worldwide, and is of major concern to health service providers. Methadone treatment for opioid dependence during pregnancy is associated with a reduction in obstetric morbidity compared to continued illicit opioid abuse. Nonetheless maternal MMT is associated with foetal growth restriction, and increased risk of preterm birth compared with no opioid use during pregnancy. Further, 50 – 90% of ME infants experience NAS. Methadone-exposed children's neurodevelopmental outcomes beyond the neonatal period are purportedly at double jeopardy

due to potential direct and indirect effects of maternal MMT during pregnancy on prenatal brain development and infant clinical outcomes, followed by the possibility of being raised in a high-risk caregiving environment characterised by a number of maternal psychosocial risk factors and their impact on parenting capacity.

CHAPTER 2

Neurodevelopmental Outcomes of Children Born to Opioid-Dependent Mothers

Despite the known multiple neonatal risks associated with maternal methadone maintenance, there are few empirical follow-up investigations of ME children beyond the neonatal period. This chapter will review the existing studies examining the developmental functioning of children born to opioid-dependent mothers across three broad domains: (a) physical, (b) social-emotional, and (c) cognitive development, before focussing more specifically on educational outcomes in the following chapters. Outcomes within these domains will be considered across three developmental periods: (a) infancy (up to 24 months), (b) early childhood (3 to 5 years), and (c) middle childhood (6 to 12 years).

2.1 Literature Review Methods

Articles published in the past 25 years (January 1992 to January 2017) were identified through the following databases: MEDLINE/PubMed, PsycINFO, PubPsych and Google Scholar. The following keywords in various combinations were utilised in the online literature search: *prenatal, exposure, drug, substance, dependency, addiction, pregnancy, child, development, neurodevelopment, outcome, physical, motor, social, emotional, behavior, cognition, cognitive, methadone, opioid, and opiate*. Reference lists were also hand-searched for additional articles. Articles were selected for review if they met the following four selection criteria: 1) peer-reviewed English language publication, 2) participants included any opioid-exposed children and a non-exposed comparison group, 3) included infants or children up to age 12 years, and 4) included a measure of physical/psychomotor, social-emotional, or cognitive development.

The initial aim was to review empirical articles reporting ME children's neurodevelopmental outcomes. However, due to a lack of studies, the literature search was expanded to include studies of illicit opioid-exposed children, hereafter referred to as OE children. Methadone and other opioids are chemically similar, and thus any neurochemical effects on the prenatally exposed child would be expected to be similar. However, as described in Chapter 1, prenatal illicit opioid use is associated with increased obstetric and neonatal adversity relative to prenatal methadone treatment. Further, children born to illicit opioid abusers may be exposed to increased environmental risk compared with children whose mothers are actively engaged in treatment (Hogan, 2007). Therefore, while studies of illicit OE children may provide evidence for the possible neurodevelopmental outcomes of ME children, the potential differences between the populations must also be kept in mind. Distinctions between studies that included ME vs. those that included other OE children are made throughout the review where necessary.

A total of 17 studies were identified, representing nine unique cohorts. The following sections summarise the children's physical, social-emotional and cognitive outcomes. Studies included in the review are also summarised in Tables 2.1 to 2.3 including a description of each study's design, sample age, size, retention, measures, main findings, and limitations. Where possible, effect sizes (Cohen's *d*) were calculated by the current author to compare between-group differences across studies, with 0.2, 0.5, and 0.8 indicating small, medium, and large effects, respectively.

2.2 A Summary of Methadone and Other Opioid-Exposed Children's Neurodevelopmental Outcomes

2.2.1 Physical outcomes. Physical health and well-being refers to a child's overall physical condition, including their nutritional intake, growth, vision and hearing, and the

presence or absence of physical illness (Santrok, 2014). It also refers to their psychomotor skills, which are skills that connect thoughts with movements (Cioni & Sgandurra, 2012). These include both the gross motor skills that develop from early infancy, such as head and limb movements, rolling over, and locomotion, as well as the fine motor skills such as grasping and manipulating objects that become more fine-tuned in early childhood as children's dexterity improves (Bayley, 1969; McCarthy, 1972; Santrok, 2014).

General population studies have shown that children's overall physical health and well-being has important educational implications. Children with poor health may have lower educational achievement due to increased school absence rates (Fowler, Davenport, & Garg, 1992; Morrissey, Hutchison, & Winsler, 2014; Pritchard, Bora, Austin, Levin, & Woodward, 2014), increased fatigue, lack of sleep, and pain, that interfere with concentration and memory (Den Wittenboer, 2000; Singh, Uijtdewilligen, Twisk, Van Mechelen, & Chinapaw, 2012). Children with hearing, vision, and co-ordination disabilities will also experience poorer achievement (Davis, Ford, Anderson, & Doyle, 2007; Roberts, Lim, Doyle, & Anderson, 2011). Visual and auditory perception across childhood is necessary to identify letters and numerals for reading and mathematical skill acquisition (Dehaene, 2011; Galotti, 2016; Wolf, 2007). Further, children's ongoing visual-motor integration skill development is necessary for decoding and writing symbols; a critical aspect of literacy and numeracy development (Carlson, Rowe, & Curby, 2013; Son & Meisels, 2006).

Table 2.1 summarises studies describing the physical outcomes of children born to opioid-dependent mothers. Two studies assessed ME and non-ME comparison infants' physical growth. Hunt, Tzioumi, Collins, and Jeffery (2008) found that ME children were significantly shorter than non-ME children at both 18 months and 3 years of age, with this effect remaining even after taking into account maternal height, maternal smoking in pregnancy, and infant gestational age. In contrast, no between-group differences in children's

weight or head circumference has been found at 6 (McGlone & Mactier, 2015) or 18 months (Hunt et al., 2008). In terms of visual development, McGlone et al. (2014) found higher rates of nystagmus (11%), strabismus (25%), and reduced visual acuity among 6-month-old ME compared with non-ME infants. In addition, 40% of ME compared to less than 1% of non-ME infants failed a standardised visual assessment.

Nine studies investigated ME or illicit OE children's psychomotor development. The Bayley Psychomotor Development Index during infancy (0 to 3 years) and the McCarthy Scales during early childhood (3 to 6 years) were the most commonly used measures to assess children's fine and gross motor skills. Results from these studies have been mixed (Table 2.1, pages 21 – 22). Nonetheless the majority of studies suggest that exposed infants perform significantly less well than non-exposed infants on these tests, with slower gross muscle development for sitting, standing, jumping, and running, and slower fine muscle development for grasping, and using writing or drawing tools (Bunikowski et al., 1998; Hans & Jeremy, 2001; McGlone & Mactier, 2015; Messinger et al., 2004). Similarly, Melinder, Konijnenberg, and Sarfi (2013) found 4-year-old ME children performed significantly below non-ME children on a test that required them to copy increasingly difficult geometric figures.

Significant covariates of poor psychomotor outcome across studies were lower birth weight (Hans & Jeremy, 2001; Messinger et al., 2004), other drug exposures (McGlone & Mactier, 2015), and socio-environmental factors such as lower socioeconomic status (SES), maternal education, poor caregiver psychological well-being, and residing in foster care (Hans & Jeremy, 2001; Messinger et al., 2004).

Table 2.1

Summary of Studies Describing Physical Outcomes of Children Born to Opioid-Dependent Mothers

Study, design, location	Age(s) assessed	Participants N (% retention if applicable)	Construct assessed	Measure	Effect size (Cohen's <i>d</i>)	Results	Limitations
INFANT AND TODDLER OUTCOMES: 0 TO 3 YEARS							
McGlone et al. (2014). Prospective cohort study, UK	6 months	81 ME (79%) 26 C (52%)	Vision Growth	Atkinson test battery: Visual assessment Weight Head circumference	NC 0.39 0.29	Significant between-group difference on the Atkinson battery**. 40% of ME vs. .08% of C children failed the visual assessment (relative risk, 5:1). 11% had nystagmus, 25% had strabismus, and 22% had reduced visual acuity. NAS and other drug exposures in pregnancy were not related to visual outcome.	Poor comparison group retention to follow-up. Examiner not always blinded to group status.
McGlone & Mactier (2015). Prospective cohort study, UK	6 months	81 ME (79%) 26 C (52%)	Gross and fine motor skills	Griffiths Mental Development Scales: Locomotor Eye-Hand	NC NC	ME children had lower Locomotor and Eye-Hand scores***. Psychomotor development also significantly related to maternal poly-drug use in pregnancy.	Poor comparison group retention to follow-up. Examiner not always blinded to group status.
Hans & Jeremy (2001). Prospective longitudinal study, USA	4, 8, 12, 18, 24 months	33 ME (79%) 45 C (96%)	Gross and fine motor skills	Bayley Scales I, PDI: 4 months 8 months 12 months 18 months 24 months	0.40 0.00 0.22 0.23 0.55	Both groups' PDI scores decreased with increasing age relative to test norms. Significant between-group difference at 18 months only**. Only birth weight made a significant, independent contribution to PDI score.	Small sample size. All participants African-American.
Bunikowski et al. (1994). Prospective cohort study, Germany	12 months	34 OE (74%) 42 C (89%)	Gross and fine motor skills	Griffiths Mental Development Scales: Locomotor Eye-Hand	0.69 0.47	Significant between-group difference on the Locomotor scale only: OE children had lower scores*.	Small sample size. OE group comprised 22 ME infants and 12 OE infants. Measurement of maternal prenatal substance use not described. No covariate control. Examiner not blinded to group status.
Hunt et al. (2008). Prospective longitudinal study, Australia	18 months	79 ME (70%) 61 C (69%)	Gross and fine motor skills Growth	Bayley Scales I, PDI Weight Height Head circumference	0.17 NC NC NC	No between-group difference on PDI. ME children were shorter than C children*. This difference persisted following adjustment for maternal height, prenatal smoking and GA.	Examiner not blinded to group status.

Table 2.1 continued

Summary of Studies Describing Physical Outcomes of Children Born to Opioid-Dependent Mothers

Study, design, location	Age(s) assessed	Participants N (% retention if applicable)	Construct assessed	Measure	Effect size (Cohen's <i>d</i>)	Results	Limitations
Ornoy et al. (1996). Retrospective cross-sectional study, Israel	6 to 24 months	37 OE 47 normal C 21 low SES 13 addicted fathers	Gross and fine motor skills	Bayley Scales I, PDI: OE at home vs. OE adopted OE at home vs. C OE adopted vs. C	 0.04 0.26 0.27	No between-group differences were found between OE children either raised at home or adopted and normal C children. Low SES controls showed poorest performance compared to normal controls*.	Small sample size. Retrospective self-report of maternal prenatal substance use. No covariate control. Examiner not always blinded to group status.
Messinger et al. (2004). Prospective longitudinal study, USA	12, 24, 36 months	1227 total (88%) Specific retention rates for CE, OE and C unclear	Gross and fine motor skills	Bayley Scales II, PDI	NC	OE children had lower PDI scores at 24*** and 36 months**. Between-group differences no longer significant following control for birth weight, ethnicity, HOME score, and foster care status.	Comparison group comprised CE infants as well as non-exposed controls. 78% African-American participants.
EARLY CHILDHOOD OUTCOMES: 3 TO 6 YEARS							
Hunt et al. (2008). Prospective longitudinal study, Australia	3 years	67 OE (59%) 44 C (43%)	Gross and fine motor skills Growth	McCarthy Motor Scale Weight Height Head circumference	0.52 NC NC NC	ME children had lower motor scores, and were shorter than controls*. Height differences persisted following adjustment for maternal height, prenatal smoking and infant GA.	Poor sample retention to follow-up. More male ME children at follow-up (58% vs. 38%). Examiner not blinded to group status.
Melinder et al. (2015). Prospective longitudinal study, Norway	4 years	26 ME/BE (68%) 23 C (64%)	Visual-motor integration	Bender-Gestalt Test II: Copy subtest	1.23	ME children had lower visual-motor integration scores***. Significant predictors of visual-motor integration included prenatal opioid exposure and smooth visual object tracking ability*.	Small sample size.
Ornoy et al. (1996). Retrospective cross-sectional study, Israel	3 to 6 years	20 OE 23 normal C 29 low SES 30 addicted fathers	Gross and fine motor skills	McCarthy Motor Scale: OE at home vs. OE adopted OE at home vs. C OE adopted vs. C	 1.17 0.37 -0.85	OE children in maternal care had lower psychomotor performance than adopted OE children*.	Retrospective self-report of maternal prenatal substance use. No covariate control. Examiner not always blinded to group status.

Note. ME = methadone-exposed; C = comparison group; OE = illicit opioid-exposed; CE = cocaine-exposed; BE = buprenorphine-exposed; UK = United Kingdom; USA = United States of America; PDI = Psychomotor Development Index; NAS = neonatal abstinence syndrome; GA = gestational age; SES = socioeconomic status; HOME = Home Observation for Measurement of the Environment Inventory.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Cohen's *d* effect size definitions: small = 0.2; medium = 0.5, large = 0.8, NC = could not be calculated.

2.2.2 Social-emotional outcomes. Behaviours that characterise children's social-emotional adjustment include appropriate interactions with teachers and peers, exerting self-control, and regulating emotions (High, 2008; McClelland, Morrison, & Holmes, 2000; Pritchard et al., 2014). Investigations examining ME and illicit OE children's social-emotional adjustment have typically focussed on assessing their internalising and externalising behaviour. Internalising problems are internally-directed behaviours such as fear, worry, somatisation, sadness, and social withdrawal (Eisenberg et al., 2001; Masten et al., 2005; Stone, Otten, Engels, Vermulst, & Janssens, 2010). Externalising problems are disruptive and antisocial behaviours including aggression, anger, irritability, non-compliance, inattention and hyperactivity (Boeldt et al., 2012; Eisenberg et al., 2001; Mathiesen, Sanson, Stoolmiller, & Karevold, 2009). Fewer than 5% of NZ children between 2 to 14 years of age demonstrate persistent patterns of symptomology characteristic of an internalising or an externalising disorder (Church, 2003; Ministry of Health, 2015, 2016).

Internalising and externalising behaviour problems have a negative impact on children's educational success. Children's internalising symptoms are proposed as interfering with learning by negatively affecting cognitive processes such as encoding and retrieval, attentional focus and task persistence (Goldschmidt, Richardson, Cornelius, & Day, 2004; Maughan, Rowe, Loeber, & Stouthamer-Loeber, 2003). Externalising problems such as inattention, hyperactivity, impulsivity, or aggression lead to children spending more time off task, and less time engaging in academic learning (Chen, Rubin, & Li, 1997; Fergusson, Horwood, & Lynskey, 1993; Hinshaw, 1992b; Masten et al., 2005; Moilanen, Shaw, & Maxwell, 2010). Children with problematic disruptive behaviour are also more likely to experience social rejection and are thus even more at risk of developing a disinterest in school and experiencing a consequential indirect reduction in their achievement. Further, children with chronic conduct problems may be excluded or expelled from school, thereby

removing them from the context in which learning is fostered (Chen et al., 1997; Dishion, Patterson, Stoolmiller, & Skinner, 1991; Hinshaw, 1992b).

Four studies investigated the internalising behaviour of ME or illicit OE children. Exposed children had higher parent and teacher-rated internalising problem scores compared to non-exposed children from age 2 to 12 years (Bada et al., 2011; Nygaard, Slinning, Moe, & Walhovd, 2016; Ornoy et al., 2001; Sarfi, Sundet, & Waal, 2013). Effect sizes were moderate to large in magnitude (see Table 2.2, pages 25 – 26), collectively indicating that children born to opioid-dependent mothers had elevated levels of anxiety and depression symptomology than their non-exposed peers.

Six studies assessed ME or illicit OE children's externalising behaviour. Exposed children consistently had increased parent and teacher-rated externalising problem scores compared to non-exposed children from age 2 to 12 years (Bada et al., 2011; Melinder et al., 2013; Nygaard et al., 2016; Ornoy et al., 2001; Slinning, 2004), and the effect sizes were predominantly large (Table 2.2, pages 25 – 26). Ornoy et al. (2001) also reported high rates of ADHD among OE children in maternal care (54%) and adopted (21%). Findings collectively suggest that prenatally ME and OE children demonstrate meaningfully higher levels of aggression, non-compliance, disruptive behaviour, and inattention than non-exposed children.

The extent to which prenatal opioid exposure was related to children's social-emotional problems differed across studies following covariate adjustment. Opioid group status, male sex, and socio-environmental risks were among the factors predicting children's problems. Findings suggested a complex interplay of prenatal and environmental mechanisms in influencing these children's social-emotional adjustment outcomes.

Table 2.2

Summary of Studies Describing Social-Emotional Outcomes of Children Born to Opioid-Dependent Mothers

Study, design, location	Age(s) assessed	Participants N (% retention if applicable)	Construct assessed	Measure	Effect size (Cohen's <i>d</i>)	Results	Limitations
INFANT AND TODDLER OUTCOMES: 0 TO 3 YEARS							
Sarfi et al. (2013). Prospective longitudinal study, Norway	24 months	33 ME (97%) 35 C (97%)	Internalising behaviour Externalising behaviour	CBCL: Internalising Externalising Total problems	0.76 0.56 0.84	ME infants had higher internalising** and externalising* problem scores. Group status not a significant predictor of outcome. Maternal psychological distress most strongly contributed to total behaviour scores, followed by male sex, and child-related parent stress.	Single-informant (maternal) reporting of children's outcomes.
Slinning (2004). Prospective longitudinal study, Norway	24 months, 4.5 years	42 OE (54%) 50 C (86%)	ADHD symptoms	CBCL Attention: 2 years: PR 4.5 years: PR, TR ADHD rating scale: 4.5 years: PR, TR	0.66 0.68, 1.05 0.82, 0.89	OE children had higher attention problem scores at 2 years*, and 4.5 years***. Between-group differences remained significant after covariate control (GA & birth weight). OE boys had greatest attention/hyperactivity problems on the teacher CBCL**.	Maternal self-report of prenatal substance use.
EARLY CHILDHOOD OUTCOMES: 3 TO 6 YEARS							
Melinder et al. (2015). Prospective longitudinal study, Norway	4 years	26 ME/BE (68%) 23 C (64%)	Attention	CBCL Attention	0.82	Exposed children had significantly higher attention problem scores**. Attention problems not correlated with NAS symptoms or opioid dose.	Small sample size. Between-group differences not adjusted for covariate effects. Single-informant (maternal) reporting of children's outcomes.
MIDDLE CHILDHOOD OUTCOMES: 6 TO 12 YEARS							
Bada et al. (2011). Prospective longitudinal study, USA	7, 9, 11, 13 years	1028 total (74%) Specific retention rates for CE, OE and C unclear	Internalising behaviour Externalising behaviour Attention	CBCL: PR, TR	NC	Significant predictors of behaviour and attention problems were prenatal opioid exposure, caregiver depression, postnatal cigarette and alcohol use, lower HOME scores, exposure to community violence and male sex*.	OE infants also had prenatal cocaine exposure. Retained participants mostly African-American (80%).

Table 2.2 continued

Summary of Studies Describing Social-Emotional Outcomes of Children Born to Opioid-Dependent Mothers

Study, design, location	Age(s) assessed	Participants N (% retention if applicable)	Construct assessed	Measure	Effect size (Cohen's <i>d</i>)	Results	Limitations
Nygaard et al. (2016). Prospective longitudinal study, Norway	8.5 years	57 OE (79%) 47 C (81%)	Internalising behaviour Externalising behaviour Attention ADHD symptoms	CBCL Internalising: PR, TR Externalising: PR, TR Attention: PR, TR ADHD Rating scale: PR, TR	 0.58, 0.40 0.74, 0.57 1.00, 0.72 1.04, 0.74	OE children had higher internalising, externalising and attention problems on the CBCL**, and higher parent*** and teacher** rated ADHD symptomology. Significant between-group differences in externalising and attention problems remained after controlling for age, sex, SES, GA and birth weight. 0% met ADHD criteria.	Maternal self-report of prenatal substance use.
Ornoy et al. (2001). Retrospective cross-sectional study, Israel	6 to 12 years	31 OE in maternal care 34 OE adopted 30 normal C 32 low SES 33 addicted fathers	Internalising behaviour Externalising behaviour ADHD	CBCL Internalising: OE at home vs. adopted OE at home vs. C OE adopted vs. C Externalising: OE at home vs. adopted OE at home vs. C OE adopted vs. C Conners Scale: OE at home vs. adopted OE at home vs. C OE adopted vs. C	 0.66 1.08 0.43 0.57 1.65 1.40 0.54 1.75 1.11	OE children in maternal care had higher internalising***, externalising*** and ADHD* problems than normal C children, and higher externalising and ADHD problems than adopted OE children*. Adopted OE children had significantly higher externalising** and ADHD problems* than normal C children. 54% of OE children raised at home had ADHD compared to 21% of adopted OE children, 21% of low SES controls and 24% of children born to addicted fathers. No normal controls had ADHD.	Wide age range aggregated. Retrospective maternal self-report of prenatal substance use. No covariate control. Single-informant (caregiver) reporting of children's outcomes.

Note. ME = methadone-exposed; C = comparison group; OE = illicit opioid-exposed; CE = cocaine-exposed; BE = buprenorphine-exposed; USA = United States of America; PR = parent-report; TR = teacher-report; GA = gestational age; SES = socioeconomic status; HOME = Home Observation for Measurement of the Environment Inventory; NAS = neonatal abstinence syndrome; CBCL = Child Behavior Checklist; ADHD = attention-deficit/hyperactivity disorder.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Cohen's *d* effect size definitions: small = 0.2; medium = 0.5, large = 0.8, NC = could not be calculated.

2.2.3 Cognitive outcomes. Cognition refers to a number of interrelated mental functions involved in thinking and information processing that develop across the lifespan (Santrok, 2014). It refers to processes in the realms of perception, memory, attention, and language which are continuously developing from early infancy, and those observed to develop more dramatically from early childhood including problem solving, reasoning, working memory, and attentional and inhibitory control (Galotti, 2016). Optimal cognitive development during infancy and early childhood is critical for children to undertake the new learning that occurs in the school setting, where formal literacy and numeracy instruction begins (Galotti, 2016; High, 2008). Reading and mathematics are inherently cognitive skills that draw on functioning within these other cognitive realms (Church, 2015; Dehaene, 2009, 2011; Galotti, 2016; Wolf, 2007).

The majority of the reviewed studies employed global measures of cognition, such as the Bayley Scales to examine ME and illicit OE infant's general cognitive development (Table 2.3, pages 30 – 31). Exposed infants had lower Bayley Mental Development Index (MDI) scores than non-exposed infants, demonstrating poorer overall perception, memory, problem solving, general knowledge and language skills (Bunikowski et al., 1998; Hunt et al., 2008; McGlone & Mactier, 2015; Nygaard, Moe, Slinning, & Walhovd, 2015; Ornoy et al., 1996). Intelligence measures (IQ tests) have been predominantly used to examine these children's cognition in early and middle childhood (3 to 12 years). Exposed children reportedly have lower mean IQ scores than their non-exposed peers (see Table 2.3, pages 31 – 33), showing poorer perceptual and verbal reasoning (Hunt et al., 2008; Konijnenberg & Melinder, 2015; Nygaard et al., 2015; Ornoy et al., 2001; Salo et al., 2009).

The magnitude of the observed between-group differences in MDI and IQ scores varied across the reviewed studies, with effect sizes ranging from 0.1 to > 2.0 (Table 2.3, pages 30 – 33). This did not appear to be related to whether the study included ME or other

OE children. Of note is that exposed groups of children generally score within 1 standard deviation (SD) of the normative mean, suggesting at least average general cognitive ability. However, ME children have been reported to evidence poorer development than their non-ME peers across more specific cognitive domains, specifically executive functioning and language development.

Executive functions are higher-order cognitive processes that include working memory, attentional control, and behavioural inhibition (Clark, Pritchard, & Woodward, 2010; Pratt, McClelland, Swanson, & Lipscomb, 2016; Roberts et al., 2011; Zelazo & Carlson, 2012). Konijnenberg and Melinder (2015) found that 4-year-old children born to mothers treated with methadone or buprenorphine during pregnancy performed significantly less well than their non-exposed peers on executive functioning measures (Table 2.3, page 32). Such findings may have direct implications for ME children's ability to master reading and mathematics skills when they start school. In addition, the behaviour governed by these skills, also referred to as children's approaches to learning, will indirectly affect their school learning through increased difficulty with paying attention, staying on task, working independently, and organising their work (Clark et al., 2010; High, 2008; McClelland & Cameron, 2011; Woodward, Lu, Morris, & Healey, 2016).

Four studies measured ME or OE children's language outcomes. Language refers to the comprehension and production of speech; beginning with the ability to distinguish between and produce different language sounds in the first year of life (Hoff, 2014), followed by a dramatic increase in vocabulary use and understanding from the second year of life through to school age (Anglin, Miller, & Wakefield, 1993; Galotti, 2016). Only one study failed to find a between-group difference in OE and non-OE infant's language development (Bunikowski et al., 1998). Moderate to large differences were reported in the remaining studies (Table 2.3, pages 30 – 31), with ME and OE children scoring below their non-

exposed peers on receptive and expressive language skills to 3 years (Hunt et al., 2008; McGlone & Mactier, 2015; Salo et al., 2009). These results suggest that children born to opioid-dependent mothers have lower overall language abilities than typically-developing children by school entry, that may negatively impact their reading and mathematics skill acquisition (Church, 2015; Hart & Risley, 1995; Hassinger-Das, Jordan, & Dyson, 2015; Scarborough, 2009; Walker, Greenwood, Hart, & Carta, 1994).

The extent to which prenatal opioid exposure, infant clinical factors and socio-environmental factors were associated with children's general cognitive, executive functioning, and language development differed across the reviewed studies. Lower scores across cognition measures were associated with socio-environmental disadvantage over and above prenatal opioid and other drug exposures in the majority of studies (Hans & Jeremy, 2001; Konijnenberg & Melinder, 2015; Messinger et al., 2004; Ornoy et al., 1996; Ornoy et al., 2001). Others found that controlling for infant clinical outcomes (e.g. gestation), maternal social background (age, education, SES), and parenting behaviour attenuated, but did not fully explain, the association between opioid group status and lower cognition scores (Konijnenberg et al., 2016; Salo et al., 2009). In one study, Nygaard et al. (2015) found significant between-group differences in illicit OE and non-OE comparison children's IQ scores despite adequate control for between-group infant clinical and environmental differences.

Table 2.3

Summary of Studies Describing Cognitive and Language Outcomes of Children Born to Opioid-Dependent Mothers

Study, design, location	Age(s) assessed	Participants N (% retention if applicable)	Construct assessed	Measure	Effect size (Cohen's <i>d</i>)	Results	Limitations
INFANT AND TODDLER OUTCOMES: 0 TO 3 YEARS							
McGlone & Mactier (2015). Prospective longitudinal study, UK	6 months	81 ME (79%) 26 C (52%)	General cognition Language	Griffiths Mental Development Scales: Performance Hearing and language	NC NC	ME infants had significantly lower cognition and language scores***. Maternal poly-drug use in pregnancy was not a significant covariate.	Poor comparison group retention to follow-up. Examiner not always blinded to group status.
Hans & Jeremy (2001). Prospective longitudinal study, USA	4, 8, 12, 18, 24 months	33 ME (79%) 45 C (96%)	General cognition	Bayley Scales I, MDI: 4 months 8 months 12 months 18 months 24 months	 0.22 0.20 0.14 0.54 0.32	ME infants had significantly lower MDI scores at 18 months only**. Cumulative socio-environmental risk (maternal education, SES, psychological well-being, IQ and parenting behaviour) was significantly associated with lower MDI scores.	Small sample size.
Bunikowski et al. (1994). Prospective cohort study, Germany	12 months	34 OE (74%) 42 C (89%)	General cognition Language	Griffiths Mental Development Scales: Performance Hearing and language	 0.65 0.20	OE infants had significantly lower cognition*, but not language scores. Within the exposed group, ME infants had better cognitive and language development than illicit OE infants*. Maternal age and SES not related to outcome over and above maternal prenatal drug use.	Small sample size. Measurement of maternal prenatal substance use not described. Exposed group comprised 22 ME infants and 12 OE infants. Examiner not blinded to group status.
Hunt et al. (2008). Prospective longitudinal study, Australia	18 months	79 ME (70%) 61 C (69%)	General cognition	Bayley Scales I, MDI	0.84	ME infants had significantly lower MDI scores***.	No covariate control. Examiner not blinded to group status.
Nygaard et al. (2015). Prospective longitudinal study, Norway	12, 24 months	65 OE (90%) 55 C (94%)	General cognition	Bayley Scales II, MDI: 12 months OE vs. C girls OE vs. C boys 24 months OE vs. C girls OE vs. C boys	 0.24 0.87 0.11 1.00	OE boys' cognitive performance significantly below controls***. No effect found for girls at age 12 or 24 months.	Maternal self-report of prenatal substance use. Examiners not blinded to group status.

Table 2.3 continued

Summary of Studies Describing Cognitive and Language Outcomes of Children Born to Opioid-Dependent Mothers

Study, design, location	Age(s) assessed	Participants N (% retention if applicable)	Construct assessed	Measure	Effect size (Cohen's <i>d</i>)	Results	Limitations
Ornoy et al. (1996). Retrospective cross-sectional study, Israel	6 to 24 months	37 OE 47 normal C 21 low SES 13 addicted fathers	General cognition	Bayley Scales I, MDI: OE at home vs. OE adopted OE at home vs. C OE adopted vs. C	0.87 1.24 0.20	OE infants in maternal care had lower MDI scores than adopted OE infants and normal C infants*. Environmental controls (low SES & children of addicted fathers) had significantly lower MDI scores than both groups of OE infants*	Small sample size. Wide age range aggregated. Retrospective report of maternal prenatal substance use. No covariate control. Examiner not always blinded to group status.
Messinger et al. (2004). Prospective longitudinal study, USA	12, 24, 36 months	1227 total (88%) Specific retention rates for CE, OE and C unclear	General cognition	Bayley Scales II, MDI	NC	Low infant birth weight, low maternal vocabulary, and foster care were associated with lower MDI scores, over and above opioid-exposure.	Comparison group comprised CE infants as well as non-exposed infants. 78% participants African-American.
EARLY CHILDHOOD OUTCOMES: 3 TO 6 YEARS							
Hunt et al. (2008). Prospective longitudinal study, Australia	3 years	67 ME (59%) 44 C (43%)	IQ Language	SBIS Reynell Language Scales: Expression Comprehension	0.53 0.69 0.59	ME children had significantly lower IQ scores**, language expression and language comprehension*.	Poor sample retention to follow-up. More male ME children at follow-up (58% vs 38%). No covariate control. Examiner not blinded to group status.
Salo et al. (2009). Prospective longitudinal study, Finland	3 years	21 OE (75%) 7 maternal care, 14 adopted 13 C	General cognition Language	Bayley Scales III, Cognitive Index: OE at home vs. C OE adopted vs. C Language Index: OE at home vs. C OE adopted vs. C	2.58 1.38 2.75 1.80	OE children had lower cognitive**and language*** scores before and after controlling for birth weight, GA, maternal age, SES, and number of caregiver placements. Cognitive outcome also associated with GA. Language outcome associated with GA and maternal self-efficacy.	Small sample size. Comparison children recruited at age 3 years.
Nygaard et al. (2015). Prospective longitudinal study, Norway	3, 4.5 years	71 OE (99%) 54 (93%)	General cognition IQ	Bayley Scales II, MDI: OE vs. C girls OE vs. C boys McCarthy GCI: OE vs. C girls OE vs. boys	0.19 0.90 0.50 1.17	OE boys' cognitive performance significantly below controls***. No effect found for girls at age 3 or 4.5 years.	Maternal self-report of prenatal substance use. Examiners not blinded to group status.

Table 2.3 continued

Summary of Studies Describing Cognitive and Language Outcomes of Children Born to Opioid-Dependent Mothers

Study, design, location	Age(s) assessed	Participants N (% retention if applicable)	Construct assessed	Measure	Effect size (Cohen's <i>d</i>)	Results	Limitations
Ornoy et al. (1996). Retrospective cross-sectional study, Israel	3 to 6 years	35 OE 24 normal C 29 low SES 30 addicted fathers	IQ	McCarthy GCI: OE at home vs. adopted OE at home vs. C OE adopted vs. C	 1.30 1.12 0.21	OE children in maternal care had significantly lower IQ than adopted OE children and normal controls*. Non-exposed children of low SES had the lowest mean IQ of all groups.	Small sample size. Wide age range aggregated. Retrospective report of maternal prenatal substance use. No covariate control. Examiner not always blinded to group status.
Konijnenberg & Melinder (2014); Koninjenberg et al. (2016). Prospective longitudinal study, Norway	4 years	35 ME/BE (92%) 31 C (86%)	IQ EF	WPPSI-R: Block design Comprehension Picture completion Vocabulary Animal pegs Sentences Day-Night task NEPSY: Statue Narrative memory BRIEF-P, GEC	 1.01 0.50 0.39 0.53 0.70 1.17 0.85 0.84 0.52 0.74	Exposed children had significantly lower scores on Block design*, Vocabulary*, Animal pegs***, Sentences***, the Day-Night task***, Statue***, and Narrative memory*. Mothers rated exposed children as having poorer EF behaviour on the BRIEF**. Group status did not significantly predict IQ or EF after accounting for maternal employment and education. No relationship found between IQ and NAS, opioid dose or other prenatal drug use (2015). Better quality of mother-child interactions at 12 months and 4 years predicted better vocabulary and narrative memory (2016).	Small sample size. Examiner not blinded to group status.
MIDDLE CHILDHOOD OUTCOMES: 6 TO 12 YEARS							
Nygaard et al. (2015). Prospective longitudinal study, Norway	8.5 years	55 OE (71%) 48 C (83%)	IQ	WISC-R: OE vs C Girls OE vs C Boys	 1.49 1.01	OE girls and boys had significantly lower IQ scores than controls***. Differences remained after controlling for SES, birth weight and GA for girls*** and boys*. Results unchanged when including only OE children in permanent foster care, and those with heroin versus other illicit substance exposure.	Maternal self-report of prenatal substance use. Examiners not blinded to group status.

Table 2.3 continued

Summary of Studies Describing Cognitive and Language Outcomes of Children Born to Opioid-Dependent Mothers

Study, design, location	Age(s) assessed	Participants N (% retention if applicable)	Construct assessed	Measure	Effect size (Cohen's <i>d</i>)	Results	Limitations
Ornoy et al. (2001). Retrospective cross-sectional study, Israel	6 to 12 years	31 OE in maternal care 34 OE adopted 30 normal C 32 low SES 33 addicted fathers	IQ	WISC-R: Verbal IQ OE at home vs. adopted OE at home vs. C OE adopted vs. C Performance IQ OE at home vs. adopted OE at home vs. C OE adopted vs. C	 0.45 0.50 0.11 0.16 0.62 0.38	OE children in maternal care had lower verbal and performance IQ than adopted OE * and normal C children*. Adopted OE children had a lower performance IQ than normal C children. OE children raised at home had similar IQ to children born to addicted fathers and low SES controls. All groups scored within the average range on both IQ subtests according to test norms.	Small sample size. Wide age range aggregated. Retrospective report of maternal prenatal substance use. No covariate control. Examiner not always blind to group status.

Note. ME = methadone-exposed; C = comparison group; OE = illicit opioid-exposed; CE = cocaine-exposed; BE = buprenorphine-exposed; UK = United Kingdom; USA = United States of America; GA = gestational age; SES = socioeconomic status; HOME = Home Observation for Measurement of the Environment Inventory; MDI = Mental Development Index; IQ = intelligence quotient; SBIS = Stanford-Binet Intelligence Scale; GCI = General Cognitive Index; WPPSI-R = Wechsler Preschool and Primary Scales of Intelligence – Revised; NEPSY = Neuropsychological Assessment; BRIEF-P = Behavior Rating Inventory of Executive Function – Preschool Version; GEC = Global Executive Composite; EF = executive function; NAS = neonatal abstinence syndrome; WISC-R = Wechsler Intelligence Scale for Children – Revised.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Cohen's *d* effect size definitions: small = 0.2; medium = 0.5, large = 0.8, NC = could not be calculated.

2.2.4 Summary of the findings. A review of the existing study findings suggested that ME and illicit OE infants and pre-school children show a number of neurodevelopmental difficulties. These impairments during infancy and early childhood appear to span visual development, psychomotor outcome, social-emotional adjustment, executive functioning, language, and general cognition. There is also emerging evidence for exposed children to demonstrate problems across some of these domains during middle childhood. Other pregnancy drug exposures, infant clinical and socio-environmental risks were generally shown to attenuate the between-group differences in exposed and non-exposed children's outcomes. However the specific influential factors and the extent to which they were associated with each outcome differed across studies.

2.3 Limitations of the Existing Research

A synthesis of the reviewed literature provided valuable information about the development of children born to opioid-dependent mothers. Nevertheless, working with high-risk populations presents numerous challenges to researchers. Conclusions about the neurodevelopmental outcomes of prenatally exposed children must be considered within the methodological inconsistencies and shortcomings of the existing research. Existing study limitations were largely related to: (a) sampling and retention, (b) prenatal opioid and poly-drug use measures, (c) measurement of, and adjustment for, additional covariates, (d) reliability of the outcome measures, and (e) the paucity of studies of children's development during the middle childhood period. A description of each of these issues is provided below.

2.3.1 Sample recruitment and retention. Recruiting large samples is a key challenge for researchers studying children born into high-risk families. Many studies investigating ME and other OE children's neurodevelopmental outcomes were therefore limited by small sample sizes, with most researchers assessing fewer than 40 exposed

children (Bunikowski et al., 1998; Hans & Jeremy, 2001; Konijnenberg et al., 2016; Melinder et al., 2013; Ornoy et al., 1996; Ornoy et al., 2001; Salo et al., 2009; Sarfi et al., 2013).

Studies that recruit small samples may have insufficient statistical power to detect significant between-group differences (Stevens, 2009) increasing the probability of Type II errors, that is, increasing the probability of “false-negative” findings. This may serve to underestimate exposed children’s developmental risk. In addition, small samples may not widely represent the population of interest. For example Hans and Jeremy (2001) had a small number of ME and non-ME participants in their study, and all participants were African-American, limiting the generalizability to a NZ population. For improved external validity, research in this field should aim to recruit large and representative samples of both ME and non-ME comparison children.

Participant retention in longitudinal follow-up research is a further challenge when studying children born to opioid-dependent mothers. Whilst investigators may succeed in recruiting large samples of exposed participants at term, as illustrated in the current study and by Lean, Pritchard, and Woodward (2013), these families are typically characterised by chaotic lifestyles and high levels of environmental instability. As such, participant attrition is common. Attrition bias may arise from high rates of participant loss during longitudinal research, whereby those at greatest risk are more likely to be lost and hence underrepresented at follow-up (Bunikowski et al., 1998; Hunt et al., 2008; McGlone & Mactier, 2015; Nygaard et al., 2015). For example, children whose caregivers have ongoing substance-use problems, poor physical and mental health, and financial and housing instability, are difficult to retain in a longitudinal study. High participant retention is crucial to reduce attrition bias, improve study generalisability and external validity. To date, there are no prospective longitudinal studies of ME children to age 9 years. This is likely due, in part, to retention difficulties.

2.3.2 Prenatal opioid and poly-drug measures. Reliance on self-report measures of maternal prenatal opioid and poly-drug use was another key limitation in a number of existing studies (Bunikowski et al., 1998; Nygaard et al., 2016; Ornoy et al., 1996; Ornoy et al., 2001; Slinning, 2004). Accurate measurement of maternal substance use during pregnancy is central to the internal validity of studies in this field, although challenging. Identifying or ruling out any neurotoxic effects of prenatal methadone exposure on children's later development is only possible if maternal methadone use, and potentially confounding poly-drug use, is accurately recorded. Investigations that rely solely on maternal self-report may be limited by recall inaccuracy, particularly in retrospective cross-sectional research studies that rely on a women's long-term memory to recall the type, frequency and amount of their drug use during pregnancy (Day & Robles, 1989). Substance use may also be underreported by women due to social stigma, or their own feelings of guilt (Kissin, Svikis, Morgan, & Haug, 2001). Testing for biomarkers, for example screening maternal urine and/or infant meconium in addition to using maternal self-reports, provides a more reliable method to confirm prenatal substance exposure (Day & Robles, 1989; Jacobson & Jacobson, 2005; Lester et al., 2001; Wouldes et al., 2014; Wouldes et al., 2004).

2.3.3 Additional covariate measurement. Limitations regarding the measurement of, and adjustment for, confounding factors in addition to poly-drug use were also identified in the existing literature. Identifying whether observed child outcomes are attributable to methadone or poly-drug exposures is challenging given the complexity of risk factors many children born to opioid-dependent mothers are exposed to. Complete accuracy in detangling the extent to which prenatal substance exposures and associated postnatal factors contribute to specific neurodevelopmental outcomes may be impossible. However, reliable and valid measurement of covariates such as gestational age, birth weight, and maternal psychosocial and other environmental risks is essential for reducing Type I errors, or "false positive"

findings. This will assist in improving what is currently understood about the developmental mechanisms that place children born to opioid-dependent mothers at risk of adverse neurodevelopmental outcomes.

Measurement and statistical adjustment for infant clinical, maternal pregnancy drug use, and maternal psychosocial and environmental risks varied across studies. One study did not include any covariate analyses, therefore it cannot be concluded that the between-group effects they found were attributable to prenatal methadone exposure (Hunt et al., 2008). Other investigations measured a limited range of confounding infant clinical and social contextual risks (Bunikowski et al., 1998; McGlone & Mactier, 2015; Nygaard et al., 2016). Two studies adjusted for potential environmental effects by comparing the outcomes of OE children raised by high-SES foster families and high SES non-OE children (Nygaard et al., 2015; Ornoy et al., 2001).

Four studies included a more comprehensive range of potential confounding and intervening factors in their analyses, including infant clinical and maternal social background factors, foster care or adoption status, and maternal mental health problems, and examined whether these factors were independent risks relating to child outcome (Bada et al., 2011; Konijnenberg & Melinder, 2015; Messinger et al., 2004; Salo et al., 2009). Hans and Jeremy (2001) employed a cumulative socio-environmental risk index summing eight dichotomised variables to determine the extent to which prenatal methadone and other substance exposures related to child outcome over and above their total level of postnatal risk.

Studies that measure and adjust for the effects of a number of covariates can draw more reliable conclusions about the extent to which prenatal opioid exposure is associated with adverse child neurodevelopmental outcomes. In addition, studies that examined the independent associations of specific covariates assist in furthering the knowledge base on

how alternative developmental mechanisms associated with maternal opioid dependence during pregnancy may contribute to children's neurodevelopmental outcomes.

2.3.4 The reliability of neurodevelopmental outcome measures. Several issues relating to the reliability of the outcome measures was identified. One issue was the use of examiners who are “blinded” to the children's group status, which is critical to avoid examiner bias. Examiners who know they are assessing substance-exposed children may be more likely to rate them as performing poorly on developmental measures (Rose-Jacobs, Cabral, Posner, Epstein, & Frank, 2002). Examiners in a number of studies were not blinded to children's group status (Bunikowski et al., 1998; Konijnenberg & Melinder, 2015; McGlone & Mactier, 2015; Nygaard et al., 2015; Ornoy, 2003). As such, the potential for examiner bias must be considered when interpreting their findings.

The use of global developmental outcome measures was a further measurement limitation of the reviewed studies. Studies typically measured children's psychomotor and cognitive development using the Bayley Scales (Bayley, 1969, 1993), or Wechsler IQ tests (Wechsler, 1974, 1989). Despite their good psychometric properties, reliance on these measures does not allow for a finer-grain assessment of children's specific psychomotor and cognitive abilities. Methadone-exposed children's lower scores on tests of visual-motor integration, executive functioning and language than their non-ME peers suggests these skill deficits may be masked when examining the results of global cognitive development and intelligence measures.

The use of standardised tests without an appropriate comparison control group raises the possibility of underestimating the rates of delay experienced by children born to opioid-dependent mothers. IQ test norms, for example, quickly become outdated due to gradual increases in the general population's cognitive ability over time, a phenomenon known as the Flynn effect (Kanaya & Ceci, 2007). Therefore, even though ME and other OE infants and

children perform within the average range according to tests norms, their cognitive development may actually be below average when compared to a representative comparison group of the same chronological age. Further caution must be taken when using internationally normed standardised measures with a cohort of NZ children, due to potential cultural differences that might affect NZ children's scores.

A further issue of generalizability is that the majority of studies compared ME and illicit OE children's cognitive outcomes with to non-exposed groups matched for low SES. A low SES comparison group may not represent typically developing children on the whole, but rather another group that would be at risk for poor outcomes. This may also explain the reason for the small between-group differences in general cognitive development or IQ in some studies. Exposed children's cognitive development should be considered in relation to an appropriate non-exposed comparison group, rather than relying on potentially outdated norms or an unrepresentative comparison group.

2.3.5 Paucity of empirical studies. A final limitation is the paucity of studies investigating prenatally ME children's outcomes during middle childhood. Potentially, effects of prenatal methadone, or other associated factors, on children's longer-term outcomes may not become apparent until the child reaches an age at which skills within the domain of interest are developing. A key issue from an ecological developmental perspective is that as ME children transition from pre-school to school age, difficulties within new domains of functioning may begin to emerge. Such sleeper effects may also be evident following the cumulative exposure to adverse environmental factors, with the compounding of risks affecting children more at school age than during early childhood (Lester, LaGasse, & Seifer, 1998; Nygaard et al., 2015).

Theories of cascading effects of impairment across domains also suggest that problems in one domain (e.g. social-emotional) will undermine functioning in one or more

other domains (e.g. educational), particularly following a developmental transition such as starting school (Masten et al., 2005; Moilanen et al., 2010). Academic skills salient to the school-age child, such as reading and mathematics, have not yet been comprehensively assessed in this population, and consequently little is known about ME children's educational achievement. It is, however, possible that ME children's elevated risk for pre-school age physical, social-emotional, and cognitive difficulties compared with typically-developing children will impact their readiness for school and subsequent achievement, as will be detailed further in the following chapter.

2.4 Chapter Summary

A review of the literature shows ME and illicit OE infants and pre-school children to have poorer physical, social-emotional and cognitive outcomes than non-exposed children. Across most studies, maternal pregnancy, psychosocial, and infant clinical risks attenuated the negative association between prenatal opioid exposure and children's outcomes. Key methodological limitations in the previous literature included small and selective samples, low retention, and inadequate measurement of confounding variables. Longitudinal follow-up of ME children through to middle childhood is necessary to examine their functioning in key developmental outcomes, including educational achievement, during this period.

CHAPTER 3

Educational Achievement

3.1 The Importance and Role of Middle Childhood Educational Achievement

Children's educational achievement during middle childhood (age 6 to 12 years) has important long-term implications for their overall educational, occupational, and psychosocial success. Educational achievement has been defined as the knowledge or skills that a child has acquired in a given academic domain, such as reading or mathematics, to a given point in time (Topor, Keane, Shelton, & Calkins, 2010). Reading and mathematics achievement in middle childhood influences performance across other academic or school domains that require literacy and numeracy skills, including writing, art, health, science, and technology (American Psychiatric Association, 2013; Ministry of Education, 2007, 2009b; Weal & Hinchco, 2010). Children with learning difficulties are affected in terms of their overall achievement, and are also more likely to evidence increased internalising and externalising symptoms and peer rejection during middle childhood (Chen et al., 1997; Cole, Martin, Powers, & Truglio, 1996; Flook, Repetti, & Ullman, 2005; Hinshaw, 1992a; Kempe, Gustafson, & Samuelsson, 2011; Lin et al., 2013; Maughan et al., 2003; Moilanen et al., 2010; Morgan, Farkas, & Wu, 2012; Willcutt et al., 2013; Wu & Kuo, 2015).

Educational underachievement and psychological maladjustment across the school years help perpetuate cycles of psychosocial disadvantage (Caspi, Wright, Moffitt, & Silva, 1998), placing children at elevated risk for dropping out of school and subsequent unemployment (Battin-Pearson et al., 2000; Cairns, Cairns, & Neckerman, 1989; Fergusson & Lynskey, 1998; Fergusson, Swain-Campbell, & Horwood, 2002; Fiester, 2013; Hernandez, 2011; OECD, 2016; Vitaro, Larocque, Janosz, & Tremblay, 2001). Further, educational delay and low adult educational attainment has been related to increased later anxiety and

depression (Fergusson, Poulton, Horwood, Milne, & Swain-Campbell, 2003; McCarty et al., 2008), illicit substance use (Townsend, Flisher, & King, 2007), and criminal offending (Farrington, Gallagher, Morley, St. Ledger, & West, 1986; Fergusson et al., 2002; Jarjoura, 1993; Reid, Patterson, & Snyder, 2002).

Research has shown that children with lower reading and mathematics skills relative to their same-age peers at school entry are more likely to have lower achievement across middle childhood and adolescence (Caro, McDonald, & Willms, 2009; Duncan et al., 2007; Pagani, Fitzpatrick, Archambault, & Janosz, 2010; Romano, Babchishin, Pagani, & Kohen, 2010). The cumulative nature of academic skill acquisition means that children who fail to acquire basic skills in reading and mathematics in the early school years may fall further behind their peers in subsequent years. Children with the requisite academic skills continue to increase their skill base, and pull further ahead of these delayed children over time (Caro et al., 2009; Cawley & Miller, 1989; Church, 2015; Morgan, Farkas, & Hibel, 2008; Tagg & Thomas, 2007). This is a phenomenon known as the “Matthew Effect” (Stanovich, 1986).

Despite the importance of early educational success on children’s current and later educational and psychosocial functioning, no empirical research to date has systematically investigated ME children’s educational outcomes at 9 years of age. However, in addition to the results of the studies reviewed in Chapter 2, data collected from an earlier follow-up assessment of the current cohort suggest evidence for educational risk amongst ME pre-schoolers (Lee, Pritchard, Austin, Henderson, & Woodward, *in preparation*). The following section describes the ME children’s school readiness at age 4.5 years.

3.2 The School Readiness of Children Born to Opioid-Dependent Mothers

School readiness refers to when a child’s development is at a level that allows them to engage in new and complex types of learning and interacting (Newman & Newman, 2017).

For children to be “ready to learn”, they must possess skills across a range of developmental domains for adapting to the demands and academic challenges of the school environment (High, 2008; Pritchard et al., 2014; Roberts et al., 2011). In addition, it is recognized in an ecological, transactional view of school readiness, that the support of parents and teachers is crucial for children to achieve this next level of development (Ansari & Gershoff, 2016; High, 2008).

The US National Education Goals Panel and the American Academy of Paediatrics have outlined five distinct, yet interrelated domains of school readiness. These include children’s physical health and well-being, social-emotional skills, approaches to learning, language, and general cognitive development (AAP Council on Early Childhood and AAP Council on School Health, 2016; Copple, 1997; High, 2008; Pritchard et al., 2014; Roberts et al., 2011). Data from the landmark Early Childhood Longitudinal Study, that included a representative US sample of 22 000 pre-school children and their families, demonstrated the importance of children’s readiness in these domains. The results showed that children with excellent health, good general and early literacy and number knowledge, and a positive approach to learning performed better in both reading and mathematics after two years of school than children that did not possess the same level of readiness. The influence of the family context was also highlighted, with children from families characterised by low-income, low maternal education, single parenthood, and non-English speaking households at risk for poor performance (Denton & West, 2002; US Department of Education National Center for Education Statistics, 2001).

Findings from the review in Chapter 2 suggest that ME pre-school children are less likely to be ready for school than typically-developing children, indicated by their relative impairment within the neurodevelopmental domains encompassed by the school readiness framework. Previous studies have however typically focused on a single, and global,

developmental outcome. The extent to which children born to opioid-dependent mothers experience multiple neurodevelopmental difficulties is less well-known. To address this issue, Lee et al. (*in preparation*) assessed children's overall school readiness. At age 4.5 years, 89 ME and 103 non-ME comparison children were assessed on physical well-being and visual-motor development, social-emotional skills, approaches to learning, language, and general cognition using a combination of caregiver report and direct child measures. A child was considered to have delay/impairment within a school readiness domain if they achieved a score below the 10th percentile of the comparison group's score distribution on the corresponding domain measure. Each of the school readiness measures employed in the 4.5-year follow-up study are also described in more detail in the current study Methods section (see Chapter 6, page 92).

The ME children had relatively higher rates of neurodevelopmental domain impairments compared with non-ME children. Specifically, 48% of ME children showed delayed physical and visual-motor development, 33% had social-emotional difficulty, 38% had poor approaches to learning, 33% had delayed language development, and 39% had delayed general cognition. In contrast between 9% and 16% of the non-ME children were impaired within one of these domains. Methadone-exposed children were also at increased risk for multiple neurodevelopmental difficulties, with 48% having multiple (≥ 2) domain impairments compared with 15% of non-ME children. Higher rates of school readiness impairment remained associated with prenatal methadone exposure following adjustment for a wide range of potential covariates, including maternal pregnancy nutrition, other pregnancy drug exposures, maternal psychosocial risks and infant medical risks. Several significant confounders, specifically male sex, low maternal education and increased maternal depression scores at birth, attenuated that association. Taken together, it is clear that children born to opioid-dependent mothers are at developmental risk during their transition to school.

More so, from a transactional school readiness perspective, children with multiple neurodevelopmental domain delays (Pritchard et al., 2014) and a multiplicity of clinical and socio-environmental risks (Denton & West, 2002; US Department of Education National Center for Education Statistics, 2001), are in jeopardy.

Against this background, this thesis aims to make a unique and important contribution to the field by assessing ME children's 9-year achievement in reading and mathematics within an ecological developmental framework. In doing so, this research will address several limitations of the previous literature by using a relatively large, longitudinally assessed cohort with good sample retention. In order to understand of the educational achievement of ME children it is first important to describe the skills required for normative, chronological age reading and mathematics achievement. The following sections describe the skills in these core academic domains that children have typically mastered by 9 years of age, the target age group of this thesis. Key variables measuring children's educational achievement that will be employed in the current study are described.

3.3 Reading at Age 9 Years

Children aged 9 to 10 years are typically described as *reading to learn*, rather than *learning to read* (Chall, 1983). By this age, they have generally been attending school for 4 to 5 years and, according to the NZ curriculum standards, should be demonstrating the ability to function as self-directed learners who are able to acquire new information through reading increasingly varied and complex texts (Church, 1999; Ministry of Education, 2007, 2009b). Children demonstrate this level of age-appropriate reading competence when they have previously acquired a complex hierarchy of fundamental component reading skills (Chall, 1983; Church, 2015; Dehaene, 2009; Wolf, 2007). These component reading skills have been described by Church (2015), and include:

1. **Comprehension.** Comprehension refers to children's ability to understand what they have read. Reading with comprehension requires children to have previously acquired: (a) an age-appropriate receptive vocabulary and knowledge of most of the words in their text, and (b) the ability to read with fluency; a level of automaticity or speed in which the meaning of the text is maintained.
2. **Fluency.** To read fluently children must have previously acquired both: (a) an adequate sight word vocabulary for rapidly recognising most high frequency words, and (b) a functional level of decoding fluency for rapidly decoding the remaining words of the text. Reading fluency typically develops at 7 to 8 years of age, when children can begin reading and understanding simple, familiar sentences and stories with increasing speed and accuracy (Chall, 1983; Duncan & Magnuson, 2011).
3. **Phonemic awareness.** For children to develop functional decoding fluency they must have previously acquired knowledge of all of the English grapheme-phoneme relationships. Children typically acquire phonemic awareness by age 5 to 6 years (Chall, 1983). Distinguishing each of the printed letters (graphemes) and their corresponding English language sounds (phonemes) is necessary to develop phonemic awareness. For many children this develops during the pre-school years.

Competent reading by 9 years is dependent on the timely development of comprehension skills, which are dependent on both vocabulary and fluency, with fluency dependent on decoding and phonemic awareness. Competent reading requires that children's decoding skills (translating written graphemes in spoken phonemes) are developed to a functional level of fluency or speed, that enables a correct response almost instantaneously and effortlessly (Church, 2015). Research has shown that phonemic decoding skills, that is,

learning that the letter *b* makes the sound “*b*” and the letter *d* makes the sound “*d*” etc., is highly correlated with word reading fluency (Shankweiler et al., 1999).

Proficient decoding skills are thus associated with increased gains made in reading progress from school entry to age 9 years (Duncan et al., 2007; Juel, 1988). In a study of 9-year-old NZ children, good readers (those reading within 12 months of their chronological age) were correctly decoding close to 70 graphemes per minute (Williams, 2002). In contrast, poor readers (those reading at a level 24 months below their chronological age) were correctly decoding fewer than 40 graphemes per minute. Other NZ studies found that interventions designed to increase poor readers’ decoding fluency to 70 correct responses per minute also subsequently improved their word reading fluency (Nixon, 2005; Zintl, 2005). American data shows that after four years of schooling, the average child can correctly read around 120 words per minute; around 15 to 25 more words per minute than children with a 12-month reading fluency delay (Hasbrouck & Tindal, 2006). Church (2015) suggests that delays in decoding fluency can be detected in children prior to age 7 years, and that interventions to improve decoding fluency need to be implemented by age 7 for high risk children to ensure they do not fall even further behind their same-age peers in literacy in their subsequent school years.

Vocabulary development is the second critical component of competent reading by age 9 years. Deriving meaning from novel passages of text is critical to reading comprehension and both requires, and cumulatively builds upon, children’s previous level of vocabulary development (Duncan & Magnuson, 2011; Rieben & Perfetti, 2013; Wolf, 2007). It is internationally and nationally established that children with insufficient receptive vocabulary for understanding increasingly complex texts will struggle with the transition to *reading to learn*. In their landmark study, Hart and Risley (1995) found that children from linguistically and financially impoverished homes had acquired fewer than half the

vocabulary words than higher SES children by 3 years of age. In a later follow-up of their study, it was found that children's 3-year vocabulary use was predictive of their 9-year language expression and reading comprehension (Walker et al., 1994). Similarly, the Dunedin Multidisciplinary Health and Development Study (Silva, Williams, & McGee, 1987) found that children with at least a 12-month language delay by age 3 years had significantly lower reading scores at ages 7, 9, and 11 years than children without early language delay. It is clear that delayed vocabulary development during the pre-school years needs to be remediated for socially disadvantaged children to develop age-appropriate reading comprehension during middle childhood.

3.4 Mathematics at Age 9 Years

Mathematics encompasses a range of subdomains that include number and algebra, geometry and measurement, and statistics (Butterworth, 2005; Dehaene, 2011; Ministry of Education, 2009a). According to the NZ curriculum standards, after at least four years of schooling 9-year-old children can typically perform single and multi-digit addition and subtraction calculations, and single-digit multiplication and division calculations. Children should be able to measure the duration of events, measure time and objects in terms of weight, height, volume or temperature, describe locations on a map, and describe and sort different two- and three-dimensional shapes. Further, children should demonstrate a basic knowledge of statistics through gathering, displaying, and interpreting simple whole-number data, and through being able to compare the likelihood outcomes of simple chance situations (Ministry of Education, 2009a).

Mastering these mathematics skills requires *number sense*, including having acquired a range of different numeracy concepts (Church, 2015; Dehaene, 2011; Hassinger-Das et al., 2015; Methe & Riley-Tillman, 2008). From a developmental perspective, learning to count is

foundational to children's understanding of number concepts (Dehaene, 2011; Nieder & Dehaene, 2009). Children typically learn the basic counting principles between ages 3 and 5 years. Following on from early counting skills, commonly learned concepts in the early school years include the names and symbols of whole numerals, ordinal number concepts such as "1st", "2nd", and "3rd", relational concepts such as "bigger", "smaller", "greater than", and "less than", measurement units such as "centimetre", and "minute", simple fractions and place value concepts, and the four core mathematical operations of addition, subtraction, multiplication and division (Church, 2015; Dehaene, 2011; Hassinger-Das et al., 2015).

Children's strategies for solving addition and subtraction problems from around age 5 to age 9 years tend to follow a typical developmental progression (Carpenter & Moser, 1984; Young-Loveridge, 2001). Counting forms the initial strategy used by 5 to 6 year-old children for solving addition and subtraction problems, before formal instruction of these operations has begun. Understanding counting principles, such as the stable count sequence, the one-to-one correspondence between the number names and the objects being counted, and the cardinality principle that the last number in a counting sequence represents the overall quantity of objects in that set allows children to answer the question "how many?" (Gelman & Gallistel, 1986; Sarama & Clements, 2009). Children typically transition from physically counting two sets of objects to using "counting-on" strategies to perform addition and subtraction operations. Counting-on involves beginning a count sequence with one number from a given problem (e.g. the 4, in $4 + 5 =$), and counting up (or down if applied to a subtraction problem) to reach the final number in the sequence (e.g. "4 [pause] 5, 6, 7, 8, 9. The answer is 9; Carpenter & Moser, 1984).

The skill of counting-on is a pre-requisite for a completely different, and more advanced understanding of part-whole relationships (Fischer, 1990; Young-Loveridge, 2001). Part-whole strategies involve splitting numbers into parts, and combining the parts together in

different ways. Derived facts or number knowledge is used to solve the mathematical problems without needing to count. Early part-whole strategies involve the splitting and combining of numbers with only one or two splits. For example, to solve “ $9 + 6$ ” a child could split the 6 into 5 and 1, join the 1 with 9 to make 10, and add the 5 with the 10 to make 15 altogether (Fuson et al., 1997; Young-Loveridge, 2001). More advanced part-whole strategies would involve larger numbers and a greater number of splits. Learning part-whole strategies allows children to think about numbers in complex and flexible ways, and to develop a number sense characterised by a wide variety of relationships (Young-Loveridge & Bicknell, 2015). Empirical research in both NZ and overseas has shown that children who were taught mathematics with an emphasis on part-whole number strategies from school entry (age 5 years) initially developed a more mature concept of number and were more successful in solving addition and subtraction word problems (Fischer, 1990; Tagg & Thomas, 2007). They also performed better on tests of overall mathematics achievement to age 9 and 10 years compared with children whose instruction had an emphasis on counting and writing numerals (Tagg & Thomas, 2007; Young-Loveridge, 2006).

In addition to a strong understanding of number relations, an adequate level of fluency with all mathematical concepts is essential for children’s mathematics achievement. The progression from counting to using part-whole strategies and number knowledge for solving the core mathematics operations is predicted by children’s fluency in naming and writing numbers, and in the rapid recognition of small quantities (Church, 2015; Mazzocco, Feigenson, & Halberda, 2011; Siders, Siders, & Wilson, 1985). Failure to acquire functional levels of fluency in early numeracy, that is, obtaining the correct answer as efficiently as possible, limits the time and cognitive energy children need to undertake more complex mathematical problems and deepen their conceptual mathematical understanding (Patterson, 2015). Church (2015) argues “if a concept such as place value is not fully developed when it

is first required, later concepts and operations which assume an understanding of place value may not be acquired. If an operation such as single digit multiplication is not practised to mastery at the point when it is first required, then later operations (such as long multiplication) which include the earlier single digit multiplication operations are unlikely to be mastered either” (p. 6).

3.5 Defining Educational Delay

Identifying children with marked difficulty in learning and applying academic skills is essential. Teachers and other education professionals can then be assisted in planning, designing and implementing specifically targeted educational services aiming to increase children’s educational achievement, and prevent the cumulative effects of educational delay. Educational delay has been assessed in the educational and developmental literature using various methods. These include children’s performance on standardised achievement tests (Goldschmidt et al., 2004; Pritchard et al., 2014; Richardson, Conroy, & Day, 1996; Wu & Kuo, 2015), teacher’s ratings of children’s achievement relative to their same-age peers (Goldschmidt et al., 2004; Masten et al., 2005; Moilanen et al., 2010; Pritchard et al., 2009), or through proxy indicators of educational delay such as enrolment in special education or learning support services at school (Hurt, Brodsky, Roth, Malmud, & Giannetta, 2005; Levine et al., 2012; Pritchard et al., 2014). The way in which these indicators of educational delay are defined in the developmental literature, and how they apply to an NZ education context are described below.

3.5.1 Standardised achievement scores. Standardised achievement tests are objective measures that are used to assess an individual’s current academic skill level in relation to a normative sample of the same chronological age (Sattler, 2001). An average achievement score on these measures is typically 100 ± 15 , with an estimated 68% of

children scoring within this range (McGrew, Woodcock, & Schrank, 2007; Wilkinson & Robertson, 2006). For 9 to 10 year-old children a standardised achievement score > 1 SD below the mean approximates an educational delay of more than 12 months below, and a score > 2 SDs below the mean approximates a delay of more than 24 months below the average child of the same chronological age (Taylor, 2000).

3.5.1.1 Specific Learning Disability. Standardised reading and mathematics tests have also been used in developmental research to identify children with specific learning disabilities. Specific learning disabilities are typically defined by moderate to severe difficulty in learning and applying one or more of the core academic skills, e.g. reading or mathematics, that is not due to severe intellectual impairment (American Psychiatric Association, 2013; Ministry of Education, 2016a; Tannock, 2013). Reading and mathematics specific learning disabilities are prevalent in between 5% and 15% of school-age children, and also commonly co-occur, with rates of comorbidity estimated to be between 30% and 70% (Willcutt et al., 2013). However the different methods used to define specific learning disabilities across research studies is likely to impact on the variation in reported prevalence rates. Several investigators have used a low achievement criterion to define specific learning disabilities in previous research. This method is used to identify children without severe intellectual impairment, typically defined as an IQ score > 2 SDs below the mean, who have achievement well below what is expected for his or her chronological age, e.g. > 1 SD below the mean on standardised achievement measures (Cavendish, 2013; Pritchard et al., 2009; Shankweiler et al., 1999; Tannock, 2013; Willcutt et al., 2013).

Children with specific learning disabilities have also been identified in past studies using an IQ-achievement discrepancy criterion (Goldschmidt et al., 2004; Morrow et al., 2006), which defines a specific learning disability as a substantial discrepancy between a child's observed and expected achievement given their intellectual ability (Fuchs & Fuchs,

2006). However, this discrepancy method has been criticised for its failure to identify educationally-delayed children that have a low, but not a severely low, IQ that are as deserving of the necessary academic intervention as children with a high IQ and delayed achievement (Jaekel & Wolke, 2014; Willcutt et al., 2013). Specific learning disability diagnoses are not used to identify children with educational delay in NZ. It is the severity of children's educational delay, for example achievement scores 1 SD vs. 2 SDs below average, and not their general intellectual ability that determines educational service eligibility in this country.

3.5.2 Teacher ratings of school achievement. These are used less often than standardised achievement tests in research for various reasons, including a lack of consistency across individual schools' or teachers' grading systems (Poskitt & Mitchell, 2012; Smaill, 2013; Thrupp, 2013). Teacher's ratings nonetheless offer helpful insights into children's achievement across a wider range of academic domains than is typically examined using standardised tests in clinical settings. Further they provide an indication of children's academic performance in an ecologically valid setting relative to the performance of their same-age peers (New Zealand Council for Education Research, 2015; Thrupp, 2013).

To identify children with educational delay in NZ schools, teachers routinely assess children's academic achievement using the schools' preferred standardised measures. Children's classroom performance is also continuously monitored across tasks that require literacy and numeracy skills. Children's classroom performance ratings incorporate a judgement about what specific reading, writing and mathematics skills they have learned, and also how they apply their literacy and numeracy skills to other curriculum areas including art, science, physical education, health and technology (New Zealand Council for Education Research, 2015; Thrupp, 2013). This multi-method assessment is employed by teachers to make biannual ratings that determine if the student is meeting the expectations of the

National Standards in literacy and numeracy. The latest national data showed that in 2016 between 15% and 25% of 9 to 10 year-old children were achieving below the National Standard in reading, writing, and mathematics (Ministry of Education, 2016b, 2016c). The proportion of children working well-below, as opposed to below, curriculum expectations for their chronological age is not currently available.

3.5.3 Special education. A number of studies have used children's special education placement as a marker for educational delay, given that children in special education have been previously screened for educational difficulties (Hurt et al., 2005; Levine et al., 2012; Pritchard et al., 2009). There are three main tiers of special education support for children with delayed literacy or numeracy in NZ. Each of these services provide in-class support for children with an educational delay to continue learning in an inclusive classroom setting (Ministry of Education, 2017a). These service levels are summarised in Table 3.1 (page 56), and are described below.

Children identified by their teacher as having high learning needs or an educational delay of more than 12-months behind their same-age peers are, in the first instance, referred for in-class support funded by the Ministry of Education's Special Education Grant (Ministry of Education, 1998). Each NZ school receives a Special Education Grant and decides, on a priority-needs basis, how these funds will be used to support their students. Schools predominantly use these funds to employ a teacher aide to support the learning of children with an educational delay. If these children do not make progress with the school-deployed support and all funds from the Special Education Grant have been exhausted attempting to support them, a referral for support from the Resource Teachers of Learning and Behaviour (RTLB) is made (Ministry of Education, 2016d). Around 2% of the NZ school population aged 5 to 18 years receive RTLB support each year (Ministry of Education, 2016d).

Resource Teachers of Learning and Behaviour are qualified teachers who provide support for students with moderate to severe learning difficulties. These students are generally working long term at level one of the NZ curriculum. For a 9-year-old child, this level of achievement indicates an 18 to 24-month educational delay. Typically, children eligible for RTLB support have additional problems such as behaviour or attendance concerns, or impaired vision or hearing. Resource Teachers of Learning and Behaviour work collaboratively with classroom teachers to develop an evidence-based intervention strategy to support the child's learning. This involves working with the teacher to differentiate and adapt the curriculum for the child's needs. The student also receives 5 hours per week of individual or group-based literacy and numeracy support, using evidence-based interventions such as *Quick60* (Chapman, 2016) to remediate reading delay, or *Numicon* (Wing, Tacon, Atkinson, & Pennington, 2015) to remediate mathematics delay. Precision teaching may also be employed for children with very specific skill deficits, for example word decoding and reading accuracy, reading fluency, reading comprehension, impaired number sense, difficulty learning and retrieving mathematics facts, or difficulty with mathematical reasoning.

Children with exceptionally high learning needs may be eligible for ongoing funding for individualised educational assistance through the government's Ongoing Resourcing Scheme (ORS; Ministry of Education, 2012). Ongoing Resourcing Scheme funding is available to 1% of the NZ school population at any given time (Ministry of Education, 2012). To meet ORS funding criteria children must have an ongoing or severe learning impairment (more than 24-months below their peers) or a language, hearing, vision, or other physical impairment. Alternatively the child must have a moderate to severe learning difficulty combined with very high difficulty in any two other need areas. Ongoing Resourcing Scheme funding is used to cover the costs of a teacher aide as well as additional specialised services, for example academic skill programmes, social skill programmes, and occupational therapy,

and any specialised equipment that an individual may require for them to continue their education in a mainstream school (Ministry of Education, 2012).

Table 3.1
Summary of the New Zealand Special Education Services

Estimated chronological age achievement level	Type of in-class support child is eligible for	Description of support service
Within 12 months of age norms	Not typically eligible	Class teacher to adapt the curriculum to meet the learning needs of the child
12 to 18 months below age norms	School-appointed teacher aide	Individual schools' provide teacher aide support for delayed children using their available resources from the Ministry's Special Education Grant
≥ 18 to 24 months below age norms/working long term at level 1 of the school curriculum	RTLB	Assistance for teachers to develop a strategy to support delayed children's learning. Small group literacy and numeracy support is also provided for 5 hours per week.
≥ 24 months below age norms/working long term at level 1 of the school curriculum	ORS	Ongoing, specialised support for children with very high learning needs and usually with other health and development difficulties. Resources for teacher aides and specialised equipment provided.

Note. RTLB = Resource Teachers of Learning and Behaviour; ORS = Ongoing Resourcing Scheme.

3.6 Chapter Summary

Middle childhood educational achievement is foundational to children's current and long-term educational and psychosocial success. Evidence from the current study cohort suggests that ME pre-school children will demonstrate difficulty acquiring reading and mathematics skills following their transition to school, placing them at high risk for educational delay. This is because children's reading and mathematics achievement by age 9

years is dependent upon the prior acquisition of a number of complex skills. Around age 9 years, children are typically described as *reading to learn*; they have an adequate level of decoding fluency and receptive vocabulary for understanding age-appropriate texts and for acquiring knowledge across a number of curriculum areas. They have also typically mastered the core operations of addition and subtraction, and are continuing to master multiplication and division operations in written calculations and applied word problems.

Developmental researchers and education professionals primarily assess children's reading and mathematics skills against chronological age norms using standardised achievement tests. Less frequently used are teacher ratings of achievement, and proxy measures of educational delay such as children's enrolment in special education services during middle childhood. Understanding how ME children perform on such educational measures will be important to establish their middle childhood educational risk. The following chapter provides a review of the literature to describe what is currently known about prenatally opioid-exposed children's middle childhood educational outcomes.

CHAPTER 4

Educational Outcomes of Prenatally Opioid-Exposed Children

As demonstrated in Chapter 2, the school-age outcomes of ME children are not known. This is despite the important role of early educational achievement, a salient school-age outcome, for children's life-long development across many psychosocial domains. Given the dearth of research relating to prenatal methadone exposure, the empirical findings of studies examining the educational outcomes of children exposed prenatally to other opioids has been reviewed below.

4.1 Literature Review Methods

A literature search was conducted to summarise the existing findings from studies investigating the educational outcomes of children born to opioid-dependent mothers. The methods outlined in Chapter 2 were also used for this review. Studies were included in the review if they met all of the following selection criteria: 1) peer-reviewed English language publication, 2) participants included prenatally opioid-exposed children and non-opioid-exposed comparison children, 3) included children between 5 and 12 years old, and 4) employed a standardised measure of educational achievement, teacher ratings of school performance, or an educational delay indicator such as enrolment in special education.

4.2 Opioid-Exposed Children's Educational Outcomes

Three studies have investigated the educational achievement of children born to opioid-dependent mothers (for a summary see Table 4.1, page 61). Only one study that assessed the reading and mathematics achievement of school-age ME children could be located, and no group differences were found between ME and non-ME children's standardised test performance (de Cubas & Field, 1993). In this study, ME and non-ME

children were matched for low SES and neonatal risk status (preterm birth, growth restriction). Taken together with low statistical power, this may explain the lack of between-group effects. In contrast, Ornoy et al. (2001) found large achievement differences in reading and mathematics scores (0.96 and 0.81 SD, respectively) between illicit OE children who were raised at home and average-SES non-OE children. However, the authors reported smaller differences in reading and mathematics scores (0.29 and 0.49 SD, respectively) between *adopted* OE children and the non-OE comparison children. Of interest, Ornoy et al.'s findings indicate that a higher family SES and the associated positive caregiving environment factors ameliorate some of the negative impacts of prenatal opioid exposure on children's reading and mathematics skills. Specific environmental intervening processes associated with OE children's poorer educational achievement could not be delineated from this retrospective study.

In a recent large-scale Australian study, Oei et al. (2017) examined the reading and mathematics achievement of OE children who were identified using National database records of their NAS diagnoses at birth. At age 9 years, OE children had significantly lower reading and mathematics achievement scores on compulsory Australian school tests than non-OE children matched for sex, gestational age, and SES. Opioid-exposed children's mean reading and mathematics scores were close to 0.6 SD below non-OE children's. Further, 10% of OE children had a reading delay and 9% had a mathematics delay, defined as scores below the National Minimum Standard. This was in comparison to 4% of the non-OE group. By age 13 years, the rates of educational delay for OE children had increased to 14% and 10% for reading and mathematics, respectively. The effect of prenatal opioid exposure on children's educational risk remained significant following adjustment for the confounding influences of younger maternal age, low parental educational attainment, indigenous ethnicity status, preterm birth (24 to 37 weeks gestation) and male sex (Oei et al., 2017).

4.3 Chapter Summary

The existing literature showed that prenatally OE children are at increased risk for middle childhood educational delay, and that their educational risk is not fully explained by confounding factors associated with maternal opioid use. Further research investigating ME children's development to school-age is required to assess their educational achievement and risk for educational delay, and elucidate the factors associated with these outcomes. Socio-environmental factors associated with educational risk for children exposed prenatally to methadone will be described in more detail in the following chapter.

Table 4.1

Summary of Studies Describing Educational Outcomes of Children Born to Opioid-Dependent Mothers

Study, design, location	Age(s) assessed	Participants N (% retention if applicable)	Construct assessed	Measure	Effect size (Cohen's <i>d</i>)	Results	Limitations
de Cubas & Field (1993). Cross-sectional study, USA	6 to 13 years	20 ME 20 C	Achievement	K-ABC: Arithmetic Reading Decoding Reading Understanding	NC NC NC	No significant between-group differences found.	Small sample size. Wide age range aggregated. Retrospective report of maternal prenatal substance use. No covariate control. Examiner not blinded to group status.
Ornoy et al. (2001). Cross-sectional study, Israel	5 to 12 years	31 OE in maternal care 34 OE adopted 30 normal C 32 low SES 33 addicted fathers	Achievement	WRAT-R Reading: OE at home vs. adopted OE at home vs. C OE adopted vs. C WRAT-R Arithmetic: OE at home vs. adopted OE at home vs. C OE adopted vs. C	 0.59 0.96 0.29 0.40 0.81 0.49	OE children in maternal care had lower reading and math scores than adopted OE children and normal C children*. No differences between adopted OE children and normal C children. OE children in maternal care performed similarly to the environmental controls (low SES controls, and children with addicted fathers).	Small sample size. Wide age range aggregated. Retrospective report of maternal prenatal substance use. No covariate control. Examiner not always blinded to group status.
Oei et al. (2017). Longitudinal database analysis, Australia	9, 11, 13 years	1688 OE 3359 C	Achievement	National Assessments: Reading: 9 years 11 years 13 years Numeracy: 9 years 11 years 13 years	 0.59 0.55 0.56 0.61 0.66 0.71	OE children had lower reading and math scores than controls at each age assessed***. Indigenous ethnicity status, male sex, preterm birth (< 37 weeks) and low parental educational attainment were related to increased risk of educational delay at each age assessed.	OE children were identified and recruited based on NAS diagnosis, and so maternal drug use was not specifically measured.

Note. ME = methadone-exposed; C = comparison group; OE = illicit opioid-exposed; USA = United States of America; K-ABC = Kaufman Assessment Battery for Children – Achievement Component; WRAT = Wide Range Achievement Test; SES = socioeconomic status.

* $p < .05$, ** $p < .01$, *** $p < .001$.

Cohen's *d* effect size definitions: small = 0.2; medium = 0.5, large = 0.8. NC = effect size could not be calculated.

CHAPTER 5

Socio-Environmental Factors That May Increase Educational Risk for Methadone-Exposed Children

Ecological theories of development maintain that children's development proceeds under the influence of a hierarchy of relevant distal and proximal processes (Belsky & MacKinnon, 1994; Bronfenbrenner, 1979; Bronfenbrenner & Morris, 1998; Ryan & Adams, 1995). It is proposed that distal biological (e.g. prenatal drug exposures, neonatal outcomes) and social-contextual (e.g. parental SES, education, ethnicity) factors would impact on children's educational outcomes through the actions of associated, more proximal family variables (e.g. parenting; Ryan & Adams, 1995). Similarly, a dual hazard systems approach to studying the impact of prenatal methadone exposure on children's later functioning would suggest that familial variables may potentially buffer these biologically vulnerable children from, or increase their risk for, neurodevelopmental impairments (Lester & Tronick, 1994). Whilst there are, to date, no empirical investigations of ME children to school-age to test this theory, evidence from studies of illicit substance-exposed children appear to support a transactional dual hazard systems approach (Levine et al., 2012; Marques, Pokorni, Long, & Teti, 2007; Oei et al., 2017; Ornoy et al., 2001).

Children's academic skill development during the intervening years from birth to middle childhood is influenced by multifactorial environmental variables on several levels. Studies employing Bronfenbrenner's Ecological Systems framework (Bronfenbrenner & Morris, 1998) have shown that these influential processes occur within the child's family, neighbourhood, and school contexts, and include how the child functions within and across those contexts (Aikens & Barbarin, 2008; Potter & Roksa, 2013; Teo, Carlson, Mathieu, Egeland, & Sroufe, 1996). This thesis will focus on the role of intervening caregiving factors

on the development of ME children's 9-year educational outcomes. Understanding the role of family processes in shaping ME children's academic skill development and educational achievement was considered one important issue to be addressed in the current study, particularly in light of the increased likelihood for these children to be raised in a high-risk caregiving environment. Factors which will be reviewed below include those related to maternal mental health and parenting.

5.1 Maternal Mental Health

It is well established that opioid-dependent mothers typically have poorer mental health and higher levels of psychological distress than the general population. Comorbid psychiatric symptomology and disorders of opioid-dependent women include stress, depression, anxiety, schizophrenia, bipolar disorder, personality disorders, and ADHD (Davie-Gray et al., 2013; Dawe, Harnett, Rendalls, & Staiger, 2003; Oei et al., 2009; Ornoy et al., 2001; Suchman, McMahon, Zhang, Mayes, & Luthar, 2006). Depression is the most prevalent mental health issue within this group of women (Arnaudo, Andraka-Christou, & Allgood, 2017). Between 30% and 45% of opioid-dependent women are reported to have clinically significant depressive symptomology (Davie-Gray et al., 2013; Sarfi et al., 2013; Wouldes & Woodward, 2010). One Australian study found that 75% of opioid and other drug-dependent women met clinical criteria for depression during pregnancy (Oei et al., 2009).

During pregnancy opioid-dependent women may, through personal and/or social pressures, attempt to abstain from using opioids. Yet, many fail to maintain abstinence (Chan & Moriarty, 2010). Using opioids despite knowledge of its potential health and social harms may elicit negative emotions in some women, thereby adversely impacting their mental health. On the other hand, opioid and other drug use has been described by patients in OST as

a way to manage mood disorders and temporarily relieve psychological distress. Many women enrolled in MMT continue to use a number of illicitly obtained drugs after pregnancy, most commonly cannabis and benzodiazepines or other sedatives, and less commonly stimulants (Davie-Gray et al., 2013; Konijnenberg & Melinder, 2015; Powis, Gossop, Bury, Payne, & Griffiths, 2000). Opioid-dependent patients have reported that their drug use provided momentary improvements in their mental state by increasing positive feelings, relieving anxiety, and filling an emotional emptiness (Melin, Eklund, & Lindgren, 2016). Importantly, psychological distress as well as methadone and other substance use have been shown to interfere with parenting capacities, as described below.

5.2 Parenting

Parental investment in their children's development is reflected in the ways in which they allocate their financial and emotional resources, time, and energy to support and enhance their child's learning and development (Gershoff, Aber, Raver, & Lennon, 2007). Often being single parents, and having higher numbers of children, methadone-maintained mothers have limited time available for talking to, playing with and subsequently educating their children. In addition, given the relatively low levels of educational attainment among this group of women, their children are likely to be exposed to qualitatively different everyday experiences than children born to more highly educated mothers (Davie-Gray et al., 2013; Hart & Risley, 1995; Suchman & Luthar, 2001). Further, without sufficient financial resources, one of a number of potential contributing factors, methadone-maintained mothers may be unable to provide their children a variety of materials or services, such as books, toys, and quality early child care that serve to enhance their cognitive development (Aikens & Barbarin, 2008; Crooks, 1995; Gershoff et al., 2007; Mol & Bus, 2011; Sirin, 2005).

Several empirical studies have reported that mothers in MMT are characterised by a detached or uninvolved parenting style. Methadone-exposed children have been shown to experience low levels of maternal sensitivity and responsiveness, with methadone-maintained mothers demonstrating a less positive affect and more detachment from their children during parent-child interaction observations (Jeremy & Bernstein, 1984; Konijnenberg et al., 2016; Maguire et al., 2016; Rasmussen et al., 2016). Methadone-maintained mothers also report that they are less involved with their child (Rasmussen et al., 2016; Suchman & Luthar, 2000). Further, this low parental involvement or disengagement is often juxtaposed by the increased risk that methadone-maintained mothers will demonstrate an authoritarian parenting style characterised by ineffective and harsh discipline, and excessive control and restriction setting (Dawe & Harnett, 2007; Dawe et al., 2003; Salo et al., 2009; Suchman & Luthar, 2000, 2001).

Children born to opioid-dependent mothers are also at increased risk of experiencing physical and sexual abuse, and neglect (Dawe & Harnett, 2007; Grella, Hser, & Huang, 2006; Hogan, 2007; Kolar, Brown, Haertzen, & Michaelson, 1994; Taplin & Mattick, 2013) that heightens their risk of longer-term neurodevelopmental problems such as educational delay (Fergusson, Boden, & Horwood, 2008; Gilbert et al., 2009; Maniglio, 2009; Norman et al., 2012). Opioid-exposed children are therefore at increased risk of social-welfare intervention and entering into foster care (Hunt et al., 2008; Moe, 2002; Nygaard et al., 2016; Ornoy et al., 1996; Salo et al., 2009; Soepatmi, 1994). Published data from the current study cohort show that approximately 44% of NZ children born to mothers enrolled in MMT during pregnancy were in out-of-home care by age 4.5 years, and those children had experienced between one and seven primary caregiver changes to that time point (Lean et al., 2013).

Following maltreatment reports to child protective services, children born to opioid-dependent mothers may be placed into stable out-of-home care that then allows them to

develop optimal behaviour and cognitive skills in a sensitive and responsive environment (McNichol & Tash, 2001; Ornoy et al., 2001). In many cases however, these children will not be permanently placed, but will experience numerous shifts between caregiving placements. Frequent primary caregiver changes are proposed as having negative effects on children's cognition, behaviour, and school adjustment due to the purportedly less sensitive caregiving and lower caregiver investment that precedes their caregiver changes. Further, children who have had multiple primary caregiver changes are likely to represent those from the most at-risk family contexts, thus they are those who were likely at increased risk for poorer outcomes prior to out-of-home care (Bada et al., 2008; Berger, Bruch, Johnson, James, & Rubin, 2009; Lean, 2012; Rubin, O'Reilly, Luan, & Localio, 2007).

5.3 The Role of the Caregiving Environment for Children's Educational Achievement.

Maternal depression and drug use, as well as exposure to uninvolved parenting styles and primary caregiver changes, contribute to the environmental adversity experienced by a large proportion of ME children. It is proposed that these children with increased risk of exposure to poor parenting and environmental deprivation have an increased risk for educational delay (Brooks-Gunn & Duncan, 1997; Gershoff et al., 2007; Goodman, 2007; Hay et al., 2001; Kiernan & Mensah, 2009; Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Shen et al., 2016). Opioid-dependent mothers enrolled in MMT during pregnancy clearly experience a complexity of socioeconomic and mental health challenges that may compromise their ability to provide an emotionally warm and cognitively stimulating home environment in which to raise their children. Although there is evidence that while many mothers enrolled in MMT do demonstrate the ability to provide good-quality and stimulating

care for their children, it is commonly to a lesser extent than mothers with greater socioeconomic and psychological resources (Davie-Gray, 2011; Konijnberg et al., 2016).

Enriched, stimulating home environments are more likely to provide support for children's timely academic skill acquisition. Caregivers who provide and participate in diverse experiences with their children in a consistent, warm emotional climate are more likely to facilitate their child's learning (Bradley, Caldwell, & Rock, 1988; Jeynes, 2010). Positive parent-child interactions, shared reading time, access to a variety of cognitively stimulating toys, and engaging in a wide range of activities both in and outside of the home are some of the childhood experiences that prepare children for formal academic instruction at school (Aikens & Barbarin, 2008; Bowey, 1995; Gershoff et al., 2007; Hart & Risley, 1995; Kainz & Vernon-Feagans, 2007; Mol & Bus, 2011; Potter & Roksa, 2013). These experiences increase children's exposure to print and language, and in turn, children become familiarised with letters and numerals, they learn language concepts that enhance reading comprehension and mathematical understanding, and they strengthen other underlying cognitive processes involved in reading, mathematics and good school adjustment such as reasoning, working memory, attentional and behavioural control (Blair, 2002; Clark et al., 2010; Dehaene, 2011; Goforth, Noltemeyer, Patton, Bush, & Bergen, 2014; Wolf, 2007).

Importantly, exposure to an accumulation of educationally-beneficial family experiences across childhood results in the most optimal educational outcomes for children (Bradley et al., 1988; Potter & Roksa, 2013; Spera, 2005; Teo et al., 1996). However, ME children are less likely than non-ME children to experience the advantages accrued from family-driven learning experiences over time. Decreased learning opportunities in the home are also suggested to impact ME children's early childhood development across numerous domains which, along with the compounding effects of exposure to adverse caregiving

environments, is likely to have an ongoing impact on their ability to acquire academic skills once they reach school age.

5.4 Chapter Summary

Maternal mental health and caregiving risks are known to be associated with children's lower educational achievement. Methadone-exposed children are more likely than their typically-developing peers to be exposed to ongoing maternal psychological problems and substance use, and the associated maladaptive parenting practices. Ecological and systems theories of development suggest prenatal substance exposure and other prenatal risks impact on child development as a function of the child rearing environment. Further research is needed to more comprehensively assess such a theory with ME children. Specifically, a methodologically sound, prospective longitudinal study with a large sample, good sample retention, and adequate measurement of confounders is needed for reliable and valid assessment of ME children's educational achievement. This will improve our understanding of the extent to which prenatal methadone exposure and/or related infant clinical and socio-environmental factors may elevate children's risk for educational delay. Knowing the malleable factors that can be targeted for intervention would assist in the early prevention efforts and educational service planning for this high-risk group of children and their families.

Aims and Hypotheses

The current study aims to address several questions concerning the middle childhood educational outcomes of children born to mothers enrolled in MMT during pregnancy.

Drawing on data from an existing prospective longitudinal study, this thesis describes the educational outcomes of ME and non-ME comparison children. The potential educational outcome influences of a wide range of term maternal psychosocial and infant variables, and socio-environmental variables measured at previous study follow-ups, will be examined. The specific aims and hypotheses for the current PhD study were as follows:

- 1. Aim:** To describe the educational outcomes of a regional cohort of children born to mothers enrolled in MMT during pregnancy, relative to a comparison group of randomly identified non-ME children at age 9 years. Specific educational outcomes examined included: (a) standardised reading and mathematics achievement (Woodcock-Johnson III Tests of Achievement [WJ-III]; Woodcock et al., 2001), (b) teacher-rated achievement across the curriculum domains of reading, mathematics, language, art, physical education, health, and technology, and (c) rates of enrolment in special education.

Hypotheses: Children born to mothers enrolled in MMT during pregnancy will have lower reading and mathematics achievement on the WJ-III than non-ME comparison children, and will have poorer teacher-rated achievement. It is expected that a significantly higher proportion of ME than non-ME children will be receiving special education at school.

- 2. Aim:** To assess the extent to which potential between-group differences in children's educational outcomes may reflect the direct effects of prenatal methadone exposure after adjusting for confounding factors correlated with maternal methadone treatment. Confounding factors examined included maternal social background, other prenatal drug exposures, infant sex, gestational age, and birth parameters.

Hypotheses: It is expected that statistical adjustment for confounding factors will attenuate the between-group differences in children's educational outcomes. It is nonetheless expected that methadone group status will remain independently associated with poorer 9-year educational outcomes following adjustment for significant confounders.

3. **Aim:** To assess whether ME and non-ME children differ on a range of caregiving factors from birth up to 9 years and whether between-group differences in caregiving factors, in turn, predict differences in children's educational outcomes. A range of intervening caregiving factors were examined. Of particular interest were the roles of children's primary caregiver changes, their caregiver's illicit drug use and psychological well-being, caregiving environment quality assessed using the HOME scale (Caldwell & Bradley, 1984), and caregiver school involvement.

Hypotheses: There will be between-group differences in children's caregiving factors, with ME children's caregiving to age 9 years characterised by increased adversity compared to non-ME children's. This, in turn, will predict poorer educational outcomes for children with prenatal methadone exposure.

CHAPTER 6

Research Design and Methodology

To address the current study aims, this thesis draws on data from the Canterbury Methadone in Pregnancy (MIP) study. The MIP study is an existing prospective longitudinal study of the neurodevelopmental outcomes of children born to mothers enrolled in MMT during pregnancy in Canterbury, NZ (Davie-Gray, 2011; Davie-Gray et al., 2013; Lee, 2012; Quick et al., 2009). This chapter provides a description of the larger longitudinal study detailing the original design, participants, and general study procedures, and then a more detailed explanation of the 9-year follow-up procedures which form the primary focus of this thesis. A description of the measures used in the current study is provided, followed by a description of how the data were managed and analysed in this thesis.

6.1 Methadone in Pregnancy Study Participants

Participants comprised two groups of children. Children were either born to mothers enrolled in MMT during pregnancy or born to non-opioid-dependent women at Christchurch Women's Hospital, Canterbury, NZ. Mothers were recruited during their third trimester of pregnancy, or at birth, between 2003 and 2008. Exclusion criteria across both groups of infants were: (a) congenital abnormality, (b) foetal alcohol syndrome, (c) HIV, (d) very preterm birth (≤ 32 weeks gestation), (e) born outside the Canterbury region, (f) born to a non-English speaking mother, and (g) mother was unable to give informed consent due to cognitive or mental health concerns. A flow diagram of the retention of participants in the study up to age 9 years is shown in Figure 6.1 below, followed by a description of both groups of study children.

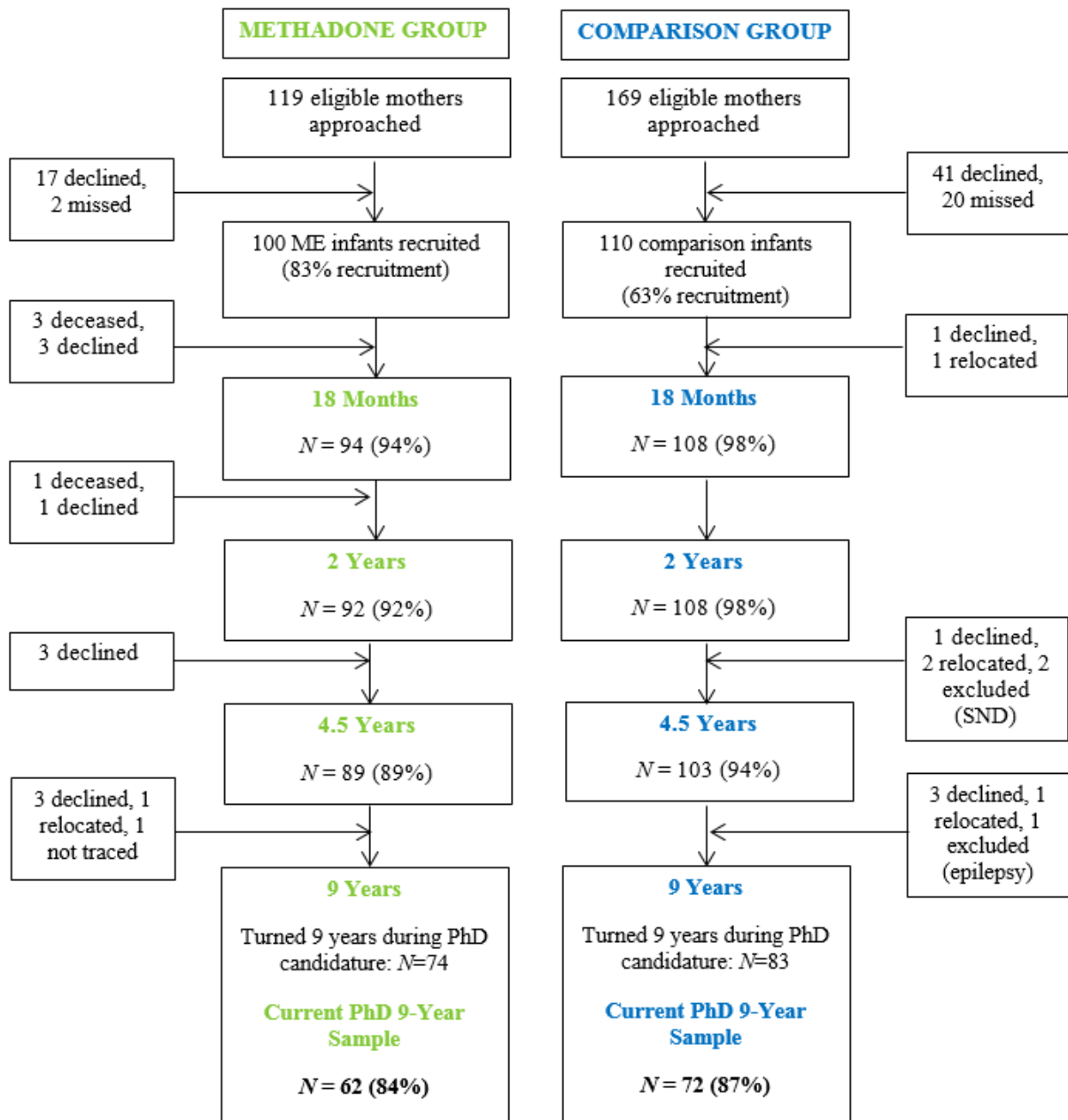


Figure 6.1. Recruitment and retention rates of participants in the Canterbury Methadone in Pregnancy Study. ME = methadone-exposed; SND = Severe neurodevelopmental delay.

6.1.1 Methadone-exposed group. The first group comprised children born to opioid-dependent women who were enrolled in the Christchurch Methadone Programme during pregnancy. The Christchurch Methadone Programme is an outpatient-based, community psychiatric service for the Canterbury region of NZ, providing both case

management and a daily methadone prescription. This programme works closely with Christchurch Women's Hospital and requires all pregnant, methadone-maintained women to attend their specialist ante-natal clinic where they receive access to MMT, specialist obstetric care and ante-natal support (Davie-Gray, 2011). Excluding five stillbirths, 119 mother-infant dyads were eligible for inclusion in the wider Methadone in Pregnancy study. Eighty-three per cent of these dyads were successfully recruited, including one set of twins ($N = 100$). Reasons for non-participation included refusals ($n = 17$) and missed recruitment ($n = 2$). As shown in Table 6.1, the recruited mothers were predominantly enrolled in MMT prior to falling pregnant or enrolled during their first trimester ($n = 77$). There were 18 women who enrolled in MMT during their second trimester and a further five in their third trimester. The mean third trimester methadone dose of the recruited mothers was $64.89\text{mg} \pm 32.09\text{mg/day}$ (range 12.5 – 195 mg/day).

Table 6.1
Profile of Methadone Use for Women in the Methadone Group

	N = 100
% first trimester enrolment	77
% second trimester enrolment	18
% third trimester enrolment	5
M (SD) third trimester daily dose, mg/day	64.89 (32.09)
Median (range) third trimester daily dose, mg/day	61.10 (12.5 – 195.00)

Participant recruitment for the current study was confined to the children turning 9 years old during the timeframe of this thesis. Therefore, only the first 74 ME children from the total cohort were eligible (i.e., old enough) to be included. Of these 74 children, 62 (84%) were included in the 9-year study. From the previous 4.5-year follow-up, an additional three families declined participation, one could not be traced, and one had relocated overseas. As shown in Table 6.2, no differences were found between ME children lost to follow-up and

those retained to age 9 years on maternal psychosocial or infant clinical characteristics at birth.

Table 6.2

Term Characteristics of the Methadone Group Participants According to Attrition

Variable	Participants (N = 62)	Non- participants (N = 12)	χ^2/t	<i>p</i>
Maternal social background				
<i>M (SD)</i> maternal age, years	29.81 (5.11)	30.92 (5.07)	-0.70	.64
% single parent (not married or cohabiting)	50.0	58.3	0.28	.60
% left school without qualifications	83.9	75.0	0.55	.46
% low family SES	93.5	91.7	.001	.98
% ethnic minority	27.4	8.3	1.99	.16
Maternal licit and illicit substance use				
% any alcohol use	21.0	-		
% any cigarette use	91.9	100.00	1.04	.31
% any cannabis use	50.0	50.0	0.00	1.00
% any benzodiazepine use	51.6	41.7	0.40	.53
% any stimulant use	25.8	16.7	0.46	.50
% any illicit opioid use	22.6	33.3	0.63	.43
<i>M (SD)</i> total drugs used	2.63 (1.39)	2.42 (0.90)	-0.51	.61
Maternal psychological well-being				
<i>M (SD)</i> EPDS score	11.47 (6.42)	11.50 (5.84)	-.02	.99
Infant clinical characteristics				
% male gender	54.8	41.7	0.70	.40
% preterm (<37 weeks)	6.5	8.3	0.06	.81
<i>M (SD)</i> gestational age, weeks	38.87 (1.61)	39.01 (1.32)	-0.28	.78
<i>M (SD)</i> birth weight z-score	-0.42 (0.74)	-0.74 (0.79)	1.34	.18
<i>M (SD)</i> birth length z-score	0.29 (1.20)	0.01 (1.05)	0.77	.45
<i>M (SD)</i> birth head circumference z-score	-0.26 (0.96)	-0.37 (1.04)	0.35	.73
% NAS treatment	87.0	83.3	0.12	.73

Note. EPDS = Edinburgh Postnatal Depression Scale; NAS = neonatal abstinence syndrome

6.1.2 Non-methadone-exposed comparison group. The second group comprised children born to mothers who reported no illicit opioid use and were not enrolled in MMT during pregnancy. Mothers with delivery dates matching those of the women in MMT were randomly identified from the Christchurch Women’s Hospital database using a random number generator (see www.randomizer.org). Of the 169 eligible comparison mothers approached, 63% were successfully recruited, including two sets of twins ($N = 110$). Reasons for non-recruitment included refusals ($n = 41$) and inability to trace at term ($n = 20$). New Zealand Census data were used to determine the regional representativeness of the recruited comparison group (Statistics New Zealand, 2006). Six social class bands from the Revised Socioeconomic Index for New Zealand (Elley & Irving, 2003) were used to categorise comparison families according to the highest-rated parental occupation in the family. Bands 1 and 2 include professional/managerial jobs, bands 3 and 4 include skilled/semi-skilled jobs and bands 5 and 6 include unskilled/labour jobs (Elley & Irving, 2003). Beneficiaries and unemployed, single mothers were also included in band 6 for this study. Figure 6.2 shows that the recruited comparison participants were representative of the Canterbury region in terms of SES.

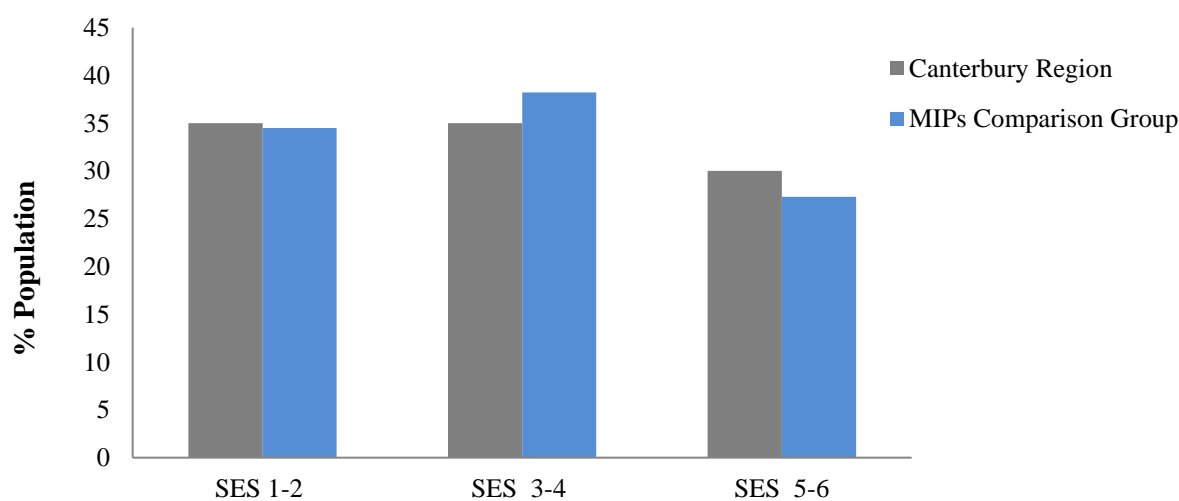


Figure 6.2. Socioeconomic status of the non-exposed comparison group at birth and Canterbury regional census data.

There were 83 non-ME comparison children turning 9 years of age within the timeframe of this thesis. Of these, 72 children and their families (87%) were included in the current study. Since the 4.5-year follow-up, an additional three declined participation, one relocated overseas and one child no longer met inclusion criteria (epilepsy). As shown in Table 6.3, the non-participants were more likely than the participants to have a mother with low educational attainment at term ($p = .006$). However, no differences in terms of other maternal psychosocial factors or infant clinical characteristics at birth were found.

Table 6.3

Term Characteristics of the Comparison Group Participants According to Attrition

Variable	Participants (<i>N</i> = 72)	Non- participants (<i>N</i> = 12)	χ^2/t	<i>p</i>
Maternal social background				
<i>M</i> (<i>SD</i>) maternal age, years	31.69 (4.94)	29.92 (6.83)	-1.09	.28
% single parent (not married or cohabiting)	9.7	8.3	0.02	.88
% left school without qualifications	15.3	50.0	7.68	.006
% low family SES	23.6	41.7	1.73	.19
% ethnic minority	22.2	16.7	0.19	.66
Maternal licit substance use				
% any alcohol use	22.2	33.3	0.70	.40
% any cigarette use	18.1	25.0	0.32	.57
Maternal psychological well-being				
<i>M</i> (<i>SD</i>) EPDS score	5.15 (4.69)	4.17 (4.30)	-0.68	.50
Infant clinical characteristics				
% male gender	47.2	41.7	0.13	.72
% preterm (<37 weeks)	5.6	8.3	0.14	.71
<i>M</i> (<i>SD</i>) gestational age, weeks	39.24 (1.65)	39.07 (1.70)	-0.33	.74
<i>M</i> (<i>SD</i>) birth weight z-score	0.09 (0.84)	0.32 (0.98)	0.86	.39
<i>M</i> (<i>SD</i>) birth length z-score	0.91 (1.09)	0.69 (1.02)	-0.65	.52
<i>M</i> (<i>SD</i>) birth head circumference z-score	0.21 (0.81)	0.22 (1.01)	0.01	.99

Note. EPDS = Edinburgh Postnatal Depression Scale.

6.1.3 Sample characteristics.

6.1.3.1 Characteristics at birth. Characteristics at birth of participants included in the current 9-year study follow-up are shown in Table 6.4. Mothers enrolled in MMT during pregnancy were younger than comparison mothers ($p = .03$), more likely to be single parents ($p < .001$), more likely to have low educational attainment ($p < .001$), and more likely to have low family SES ($p < .001$). Mothers in both groups were predominantly of European descent. Women enrolled in MMT during pregnancy were either of NZ European (73%) or NZ Māori (27%) ethnicity, whereas the ethnic diversity of the non-ME group was more representative of the Canterbury region at the time of recruitment (78% were NZ or other European, 12.5% were NZ Māori, 1.4% were Pacific Islander, and 8.3% were Asian or African; Statistics New Zealand, 2006).

Mothers enrolled in MMT were more likely to have used licit and illicit substances during pregnancy, including tobacco (92%), cannabis (45%), sedatives (29%), stimulants (21%) and additional opioids (23%, $ps < .001$). No between-group differences in alcohol use were found. Poly-drug use during pregnancy was common among methadone-maintained mothers, who used an average of 2.63 (range, 0 – 6) different substances in addition to prescribed methadone. Mothers enrolled in MMT also had significantly higher depressive symptomology in pregnancy compared to the comparison mothers ($p < .001$). There were no between-group differences in mean infant gestational age, but ME infants had lower birth weight ($p < .001$), length ($p = .002$) and head circumference ($p = .003$) z-scores than non-ME infants. The majority (87%) of the ME group infants required drug intervention treatment for NAS.

Table 6.4
Sample Characteristics during Pregnancy and at Birth

Variable	Methadone group (N = 62)	Comparison group (N = 72)	χ^2/t	<i>p</i>
Maternal social background				
<i>M (SD)</i> maternal age, years	29.81 (5.11)	31.69 (4.94)	-2.17	.03
% single parent (not married or cohabiting)	50.0	9.7	26.60	<.001
% left school without qualifications	83.9	15.3	62.92	<.001
% low family SES	93.5	23.6	66.12	<.001
% ethnic minority	27.4	22.2	0.49	.49
Maternal licit and illicit substance use				
% any alcohol use	21.0	22.2	0.03	.86
% any cigarette use	91.9	18.1	72.88	<.001
% any cannabis use	50.0	1.4	43.06	<.001
% any benzodiazepine use	51.6	1.4	45.27	<.001
% any stimulant use	25.8	1.4	17.93	<.001
% any illicit opioid use	22.6	-		
<i>M (SD)</i> total drugs used	2.63 (1.39)	0.44 (0.69)	11.22	<.001
Maternal psychological well-being				
<i>M (SD)</i> EPDS score	11.47 (6.42)	5.15 (4.69)	-6.17	<.001
Infant clinical characteristics				
% male gender	54.8	47.2	0.77	.38
% preterm (<37 weeks)	6.5	5.6	0.05	.83
<i>M (SD)</i> gestational age, weeks	38.87 (1.61)	39.24 (1.65)	-1.29	.20
<i>M (SD)</i> birth weight z-score	-0.42 (0.74)	0.09 (0.84)	-3.34	<.001
<i>M (SD)</i> birth length z-score	0.29 (1.20)	0.91 (1.09)	-3.12	.002
<i>M (SD)</i> birth head circumference z-score	-0.26 (0.96)	0.21 (0.81)	-3.08	.003
% NAS treatment	87.0	-		

Note. EPDS = Edinburgh Postnatal Depression Scale; NAS = neonatal abstinence syndrome

6.1.3.2 Characteristics at age 9 years. Characteristics at age 9 years of participants included in the current study are shown in Table 6.5. Close to 55% of 9-year-old ME children were in their biological mother's care, compared to 100% of non-ME children. The ME children who were no longer in their mother's care lived either with their biological fathers (10%), other relatives (19%) or non-relatives (16%). Methadone-exposed children's caregivers were, on average, older than non-ME children's ($p = .005$), likely due to the number of ME children in their grandparent's care. At age 9 years there were still greater numbers of single parents (58% vs. 13%, $p < .001$) and low SES families (84% vs. 17%, $p < .001$) in the methadone group.

In terms of substance use, nearly half (44%) of the ME children lived with a caregiver who was enrolled in MMT at the 9-year follow-up. This was the case for 26 of the 34 children in their biological mother's care, and one of the six children in their biological father's care. There were no between-group differences in caregiver alcohol use. Methadone-exposed children's caregivers were however more likely to use tobacco (56.5% vs. 15.5%, $p < .001$), and cannabis than comparison caregivers (32.2% vs. 1.4%, $p < .001$). The use of illicit sedatives, stimulants and other opioids was infrequently reported across both groups. Methadone-exposed children's caregivers had significantly higher depression scores than the comparison caregivers at the 9-year follow-up ($p < .001$).

At the time of their assessment, ME children were an average of 2 months older than non-ME children ($p = .02$). Both groups of children had mean IQ scores within the normal range (Wechsler, 2011), but the ME children's mean IQ score was significantly lower than the non-ME group's ($p < .001$).

Table 6.5
Sample Characteristics at Age 9 Years

Variable	Methadone group (<i>N</i> = 62)	Comparison group (<i>N</i> = 72)	χ^2/t	<i>p</i>
Caregiving arrangement				
% living with biological mother	54.8	100.00	41.11	<.001
% living with biological father only	9.7	-		
% living with other relative	19.4	-		
% living with non-relative	16.1	-		
Caregiver social background				
<i>M (SD)</i> primary caregiver age, years	45.50 (10.71)	41.22 (5.00)	2.88	.005
% single parent (not married or cohabiting)	58.1	12.7	30.46	<.001
% low family SES	83.9	16.7	60.30	<.001
% minority ethnicity	21.0	22.2	.03	.86
Caregiver licit and illicit substance use				
% enrolled in MMT	43.5	-		
% any alcohol use	45.2	57.7	2.10	.15
% any cigarette use	56.5	15.5	24.02	<.001
% any cannabis use	32.3	1.4	21.10	<.001
% any sedative use	4.8	1.4	1.37	.24
% any stimulant use	1.6	-		
% any illicit opioid use	3.2	-		
Caregiver psychological well-being				
<i>M (SD)</i> depression score*	6.34 (4.89)	2.44 (3.42)	-5.40	<.001
Child characteristics				
<i>M (SD)</i> child age, years	9.64 (0.45)	9.48 (0.34)	2.31	.02
<i>M (SD)</i> full scale IQ at 9 years	93.26 (13.10)	106.51 (13.84)	-5.67	<.001

* Depressive symptomology was measured using the Composite International Diagnostic Interview at 9 years

6.2 Canterbury Methadone in Pregnancy Study General Procedures

Methadone-exposed and non-ME children and their primary caregivers were invited to participate in MIP study follow-ups at age 18 months, 2, 4.5 and 9 years. At age 18 months, children and their caregivers were visited in their homes. Families attended the 2-year, 4.5-year and 9-year developmental assessments and caregiver interviews at the

Canterbury Child Development Research Group (CCDRG) facility at the University of Canterbury campus. The CCDRG research facility contains multiple separate rooms, including a primary assessment room, a waiting room, a video control room and a kitchen. Child assessments took place in the primary assessment room, with children sitting at a large table opposite a researcher for the majority of the assessment. Researchers were blinded to children's group status at each follow-up when possible. At the 18-month home visit, it was not possible for the visiting researcher to be blinded to children's group status, as this same researcher also interviewed the caregiver about their drug use.

Each assessment was video-recorded to ensure consistent task administration and scoring. Camera angles and zoom functions were able to be manipulated by another researcher from the control room to enable the child to be consistently in view. During the child assessments at age 2, 4.5 and 9 years, primary caregivers completed an interview in the waiting room where they could also view the live recording of the child assessment through closed-circuit television. Following each assessment, children were provided with a small gift, and their caregivers were given a \$20 grocery or petrol voucher gratuity.

6.3 Current Study Follow-Up Procedures

Ethical approval for the current study procedures was obtained from the Southern Health and Disability Ethics Committee (*Reference: URB/07/10/042, see Appendix A*). Each child's primary caregiver was contacted at 9.5 years of age +/- 4 weeks using phone numbers and addresses collected at previous follow-up study waves. Families with outdated contact information were located using medical practice records with assistance from the CCDRG Senior Research Nurse Specialist. During initial contact, a verbal explanation of the follow-up study was provided and families were invited to participate. Caregivers who agreed to participate were sent an information sheet detailing the aims of the study, a letter confirming

their appointment date and time, and a map to the CCDRG research facility. All appointments were also confirmed by phone call or text message the week of the assessment. To ensure maximum participant retention, families living within Christchurch without means of transport were driven to the assessment, and those from outside Christchurch were reimbursed with petrol vouchers, or had flights and accommodation arranged for them by the research co-ordinator.

6.3.1 Obtaining caregiver consent and child assent. Upon arrival at the research facility, primary caregivers were provided a detailed explanation of the assessment procedure, and were reassured that all study information was confidential and their anonymity would be preserved. Children and caregivers were made aware that they could withdraw from the study at any time. Following a description of study protocol the primary caregiver signed three consent forms agreeing to: (a) the participation of themselves and their child in the study, (b) the video recording of the assessment, and (c) obtaining supplementary data from the child's school teacher (see Appendix B). Oral assent was acquired from each child following a description of the tasks they would be asked to complete.

6.3.2 Developmental assessment administration. The 9-year developmental assessment battery was administered by a clinical psychologist, as well as the author and an additional postgraduate student under the supervision of that clinician. It took an average of 3.5 hours to complete all assessment measures. During the assessment children were offered several breaks, food and drink, and time to visit their caregiver in the adjacent room. Assessments were ceased, or individual tasks were omitted from the assessment battery if the child no longer wanted to participate. During the child assessment a trained CCDRG research member administered a structured interview to the child's primary caregiver. Following the child's assessment, the author sent their teacher a school performance questionnaire (see Appendix C) by mail with a self-addressed, pre-paid return envelope. Teachers were

informed that the child was participating in a child development study, and were not alerted to the fact that it was a study of prenatal methadone exposure. Teachers were therefore blinded to the child's prenatal history.

6.4 Current Study Measures

Measures for this study included standardised tests of children's reading and mathematics achievement, teacher ratings of children's achievement across the school curriculum, teacher-reports of children's special education enrolment, and a standardised IQ test. In addition to these 9-year measures, the longitudinal design of the wider MIP study allowed for the consideration of a range of potentially confounding and intervening factors. Confounding factors were considered those risks present around the time of the prenatal opioid-exposure or during the neonatal period. These included maternal social background characteristics, maternal poly-drug use during pregnancy, and infant clinical outcomes. Intervening factors were risk and resiliency factors present across childhood that potentially explained the link between prenatal methadone exposure and 9-year educational outcome. These included primary caregiver changes, ongoing caregiver illicit substance use to the 9-year follow-up, caregiver depressive symptomology from birth to age 9 years, the child's early home and caregiving environment quality, and their caregiver school involvement at age 9 years. An overview of the MIP study database is shown below (Figure 6.3), with the data used in the current study indicated in bold. A description of the specific measures used to obtain these data follows.

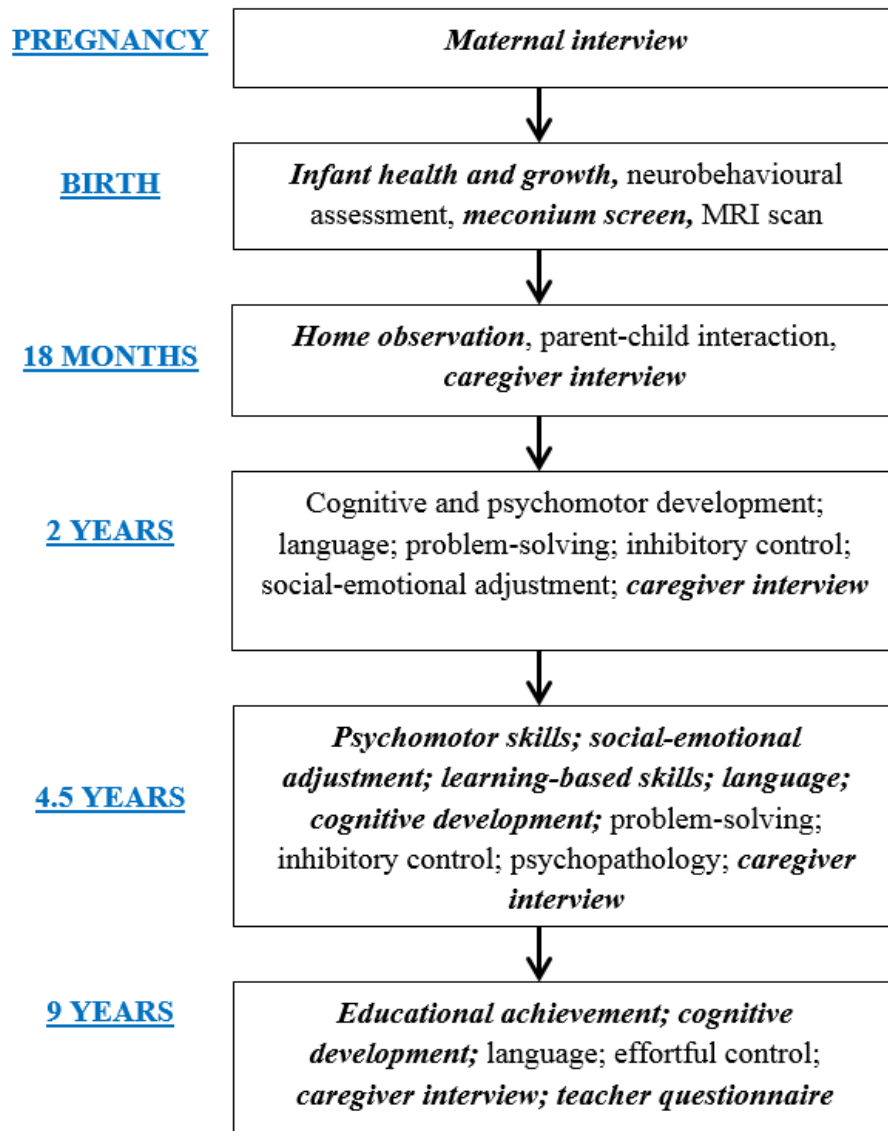


Figure 6.3. Overview of the Canterbury Methadone in Pregnancy Study database. ***Bold and italic font*** indicates data relevant to this thesis.

6.4.1 9-Year Measures.

6.4.1.1 The Woodcock-Johnson III Tests of Achievement. The WJ-III (Woodcock et al., 2001) is a standardised measure of academic achievement for individuals aged 2 to over 90 years, with norms based on a large ($n = 8,787$), randomly selected sample (Blackwell, 2001; McGrew et al., 2007). Children were administered six subtests from the WJ-III Form B, Australian adaptation.

Letter-Word Identification. This test measures children's reading decoding skills and requires children to identify and read aloud from a list of words. For children aged 9 years, items begin as three letter words, followed by longer words that are used less frequently in the English language. Children receive a score of 1 for each correctly identified and pronounced word. Children are not required to know the meanings of the words. Raw scores are calculated by summing the total number of correct items. Administration of the subtest is ceased after six consecutive errors.

Reading Fluency. This test measures the speed and accuracy with which children can read simple sentences. The test requires children to read as many statements as possible in 3 minutes. Children are provided with a pencil and the test items in the WJ-III response booklet. Children must appropriately circle Y if the statement is true or N if the statement is false. Statements do not become incrementally more difficult as the test progresses. Final raw scores are calculated as the number of correct items minus the number of incorrect items.

Passage Comprehension. This test measures children's ability to understand what they have read. Children must independently read an incomplete passage of text, and correctly identify the missing word to complete the passage. For children aged 9 years, items begin as single sentences with an accompanying illustration to assist comprehension. As the test progresses, longer, more semantically complex passages containing more difficult vocabulary are introduced. Raw scores are calculated by summing the total number of correct items. Administration is ceased after six consecutive errors.

Calculation. This test measures mathematical computation or arithmetic skills. Children are provided with a pencil and are presented with a list of written equations from the WJ-III response booklet. Items increase in difficulty as the test progresses, beginning with single-digit addition, subtraction, multiplication and division equations. Multi-digit equations using these different operations are then introduced, as are equations involving fractions,

decimals, percentages, and negative integers. Raw scores are calculated by summing the total number of correct items. The subtest is ceased after six consecutive errors.

Math Fluency. This subtest measures children's ability to solve basic facts quickly, and requires children to complete as many addition, subtraction and, as the test progresses, multiplication equations as possible within 3 minutes. The format of the equations in the WJ-III student response booklet was revised for the current study to reflect a more appropriate presentation format for children learning mathematics in NZ schools. Therefore rather than presented vertically, the equations were presented to children horizontally (e.g. $1 + 7 =$) on A4 sized paper (see Appendix D for an example). This revised test format has been used previously in NZ longitudinal research (Clark et al., 2010; Pritchard et al., 2009). Final raw scores are calculated as the total number of correct items.

Applied Problems. This test measures how well children can understand and solve orally-presented practical mathematics problems. The examiner reads each item aloud to the child who must identify the necessary mathematical operation to solve the problem, while differentiating between necessary and extraneous information required to solve the problem. For children aged 9 years, early items include problems related to basic quantitative mathematics operations, time concepts, and calculations involving money. The problems progress in difficulty to items that include more nonessential information, and items with multiple mathematics concepts and operations. Children are provided with a pencil and paper to solve the problems if they choose. Raw scores are calculated by summing the total number of correct items. Administration is ceased after six consecutive errors.

Administration time for the six reading and mathematics subtests was approximately 45 minutes. Following administration, each child's subtest scores were entered into the Compuscore Programme for the normative update of the WJ-III (Schrank, 2007). This generated subtest and composite Broad Reading and Broad Math standard scores ($M = 100$,

$SD = 15$). The six Broad Reading and Broad Math subtests have strong internal consistency reliabilities ranging from $\alpha = 0.83 - 0.92$ (Woodcock et al., 2001). Additionally, use of these cluster scores increases test validity by assessing skills in several sub-domains across the two achievement areas (Woodcock et al., 2001). The WJ-III also has good concurrent validity with moderate to high correlations between the Broad Reading and Broad Math clusters and other validated achievement tests including the Kaufman Test of Educational Achievement, and the Wide Range Achievement Test (Blackwell, 2001). This standardised measure has also been used in previous studies of substance-exposed children and other high-risk populations (Pritchard et al., 2014; Singer et al., 2008).

For the current study, an educational delay on the WJ-III was determined using a score > 1 SD below the non-ME comparison group 's mean on Broad Reading and Broad Math. A severe delay was classified as a score > 2 SDs below the non-ME group mean. These cut-offs were used to indicate children with at least a 12-month, and at least a 24-month delay, respectively, compared to their regionally-representative peers (Taylor, 2000).

6.4.1.2 Teacher ratings of achievement. Teachers rated children's achievement across seven curricular areas that included reading, mathematics, written and spoken language, art, physical education, health and technology (Ministry of Education, 2007). For each academic area, teachers indicated whether the child was: (1) more than 12-months delayed, (2) below average, (3) average, (4) above average, or (5) more than 12-months ahead relative to their classroom peers. A dichotomous variable indicating whether children were achieving either below average or more than 12-months delayed vs. those performing average to more than 12-months ahead was used in the current analysis.

6.4.1.3 Special education enrolment. Teachers also provided information concerning children's special education or learning support at school. Teachers were asked if children received support in the form of a school-funded, RTLB-funded or ORS-funded teacher aide,

and whether they were enrolled in other specialised programmes including reading or literacy, behaviour management, perceptual motor, social skills, occupational therapy, and speech and language programmes. Teacher reports of children's learning support at school were cross-checked against information provided by primary caregivers during the 9-year assessment interview.

6.4.1.4 General intelligence (IQ). The Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II; Wechsler, 2011) was used to assess children's IQ at age 9 years. The WASI-II is a brief, standardized IQ test for individuals aged 6 to 90 years, with norms based on a large ($n = 2,300$), nationally representative US sample (Irby & Floyd, 2013; McCrimmon & Smith, 2013). The WASI-II consists of four subtests that assess perceptual reasoning (Block Design, Matrix Reasoning) and verbal comprehension (Vocabulary, Similarities) to provide an estimation of each child's IQ ($M = 100$, $SD = 15$). Block Design assesses visual-spatial integration and requires children to recreate a series of 13 geometric designs using bi-coloured blocks. Matrix Reasoning assesses visual problem solving and requires children to complete a set of visual matrices that increase in pattern intricacy as the test progresses. Vocabulary measures verbal concept formation and requires children to verbally express word or concept definitions. Finally, the Similarities subtest measures verbal expression and requires children to define the relationship between two verbal concepts.

Administration time for the four subtests was between 30 and 60 minutes. The WASI-II subtests have excellent internal consistency coefficients exceeding .90, with average internal consistency and test-retest reliability coefficients of greater than .92 for the total IQ estimate (Irby & Floyd, 2013; McCrimmon & Smith, 2013). The WASI-II has good concurrent validity, correlating well (.91 to .92) with other validated full-length intelligence measures (Irby & Floyd, 2013).

6.4.2 Covariate Measures.

6.4.2.1 Maternal social background at birth. All mothers completed a comprehensive maternal lifestyles interview administered by the CCDRG Senior Research Nurse Specialist during their third trimester of pregnancy or at birth. Five maternal social background variables derived from this interview were included in the current analyses. Maternal age was recorded in whole years. Marital status was recorded as single or not (married or cohabiting). Educational attainment was classified into six categories: (1) left school between the ages 13 and 16 years with no formal qualifications, (2) left school with a level 1 qualification equivalent, (3) had further secondary education, (4) had a secretarial or trade qualification, (5) had a professional qualification, and (6) had a tertiary qualification. Family SES was recorded based on the highest rated occupation of the mother or their partner. Codes from the Elley-Irving index (see section 6.1.2, page 75) were used, with low SES assigned to families with a code of (4) or above. Finally, mothers were coded as an ethnic minority if they identified as NZ Māori, Pacific Islander, Asian or African.

6.4.2.2 Poly-drug exposures. All mothers were interviewed in confidence about their substance use and dependence during pregnancy as part of their third trimester/term interview. Detailed information on cigarette, alcohol, cannabis, benzodiazepine, stimulant and additional opioid use was collected using interview measures based on the Composite International Diagnostic Interview (WHO, 1993) and custom written items (Davie-Gray et al., 2013). In addition, some methadone-maintained mothers underwent urinary drug screens at random at their MMT antenatal clinics to confirm their pregnancy drug use. Further, meconium samples from all infants was collected at term and analysed for drug metabolites using liquid chromatography-mass spectrometry in the Department of Toxicology, Canterbury Health Laboratories. Prenatal drug exposure was recorded as positive if a mother either reported the drug use, and/or drug metabolites were detected in urine or meconium. A

prenatal poly-drug exposure variable was then created by summing the total number of different drugs that each mother used during pregnancy.

6.4.2.3 Infant clinical characteristics at birth. Infant clinical data were gathered from hospital records and included child sex, gestational age, birth weight, length and head circumference. Gestational age was recorded in weeks. The latter three growth parameter measurements were recorded in centimetres and were transformed into z-scores that adjusted the raw birth weight, length and head circumference measurements for infant sex and gestational age.

6.4.2.4 Primary caregiver changes. Children's caregivers reported who the child's mother and father figures were for each 6-month period that preceded each of their developmental assessments at 18 months, 2 years, 4.5 years and 9 years. For the current study, each child's primary caregiver was defined as the person looking after the child for the majority of the time, not necessarily the child's biological mother (Australian Institute of Family Studies, 2015). Children's total number of primary caregivers from birth to age 9 years was then summed. For example, a child who resided with their biological mother until age 6 months, who then lived with another family member until age 12 months, experienced one primary caregiver change. If the same child returned to their mother's care by age 4.5 years, they were coded as having two primary caregiver changes.

6.4.2.5 Caregiver illicit substance use. Each child's primary caregiver (not necessarily their mother) was asked to report their illicit substance use at each follow-up assessment. Any cannabis, benzodiazepine or other sedative, stimulant and additional opioid use at 18 months, 4.5 years and 9 years was recorded. A dichotomous variable indicating any caregiver use of these substances at any age assessed was created for use in the analyses.

6.4.2.6 Caregiver depression. Primary caregiver depressive symptomology was assessed at each study follow-up as a measure of psychological well-being. Maternal

depression during pregnancy and primary caregiver depression at age 18 months were assessed using the Edinburgh Postnatal Depression Scale (EPDS; Cox, Holden, & Sagovsky, 1987). The EPDS is a 10-item questionnaire, with statements including “I have felt sad or miserable” and “I have been so unhappy that I have been crying”. Statements were rated by participants on a 4-point scale, with reference to their depressive symptomology over the past 2 weeks. Item responses ranged between: (0) often, (1) sometimes, (2) hardly ever, and (3) never. Positive items were reverse coded for scoring, and total depressive symptomology scores were summed to give a full-scale score. A cut-off score of ≥ 13 on the EPDS is reported to have adequate sensitivity (79%) and specificity (85%) for identifying depression (Cox, Chapman, Murray, & Jones, 1996). The EPDS has been widely used in studies of substance-dependent women internationally (Bowen & Muhajarine, 2006; Pajulo, Savonlahti, Sourander, Helenius, & Piha, 2001; Ross & Dennis, 2009).

Primary caregiver depressive symptomology at ages 4.5 and 9 years was assessed using relevant components of the Composite International Diagnostic Interview (WHO, 1993). Caregivers responded to 20 items that assessed whether they had a period of at least two weeks over the past month when they, for example, “felt sad, blue or depressed every day”, “lost interest in most things like work, your family, hobbies etc.” Items were rated by participants as either: (1) yes, or (2) no. Total depressive symptomology scores were created by summing each positive (1) response. This depression scale had excellent internal consistency reliabilities at both 4.5 and 9 years ($\alpha = .90$). Individual depression scores at each age assessed, as well as a total score summing caregiver’s depressive symptomology scores across the child’s life, were considered for use in the analyses.

6.4.2.7 Early caregiving environment quality. The HOME (Caldwell & Bradley, 1984) was used to measure the quality and quantity of stimulation and support available to the study children in their early caregiving environment. Observations were made in each

child's home at age 18 months to assess their caregiving experiences in a naturalistic context. The HOME inventory (Infant-Toddler version) was completed through direct observation and structured interview questions with the child's primary caregiver. The HOME inventory is comprised of 45 items, with six subscales. The six subscales are emotional and verbal responsiveness of the caregiver (11 items), acceptance of suboptimal behaviour and avoidance of restriction and punishment (8 items), organisation of the physical and temporal environment (6 items), provision of appropriate play materials (9 items), parental involvement with the child (6 items), and opportunities for variety in daily stimulation (5 items). Items are scored (1) yes, or (0) no, and then summed across each of the subscales with higher scores indicating a more stimulating and supportive caregiving environment (Totsika & Sylva, 2004).

Total HOME scores, calculated by summing each of the six subscale scores, were used in the current analyses. The HOME inventory has good psychometric properties, with high internal consistency of the total score ($\alpha = .80$) and inter-observer reliability consistently reported as .80 or more (Totsika & Sylva, 2004). The HOME has been widely used in studies of high-risk children, including in research examining the educational outcomes of children born to women who used substances during pregnancy (Hurt et al., 2005; Morrow et al., 2006; Singer et al., 2008).

6.4.2.8 Caregiver school involvement. Teachers rated children's caregiver school involvement at age 9 years using four items from the Avon Longitudinal Study of Parents and Children school questionnaire (ALSPAC Study Team, 2001). Teachers responded either (1) yes, or (0) no on the following items: (1) help in class, (2) help with out-of-class activities, (3) attend parent-teacher sessions, (4) other school activity. A total school involvement score was created for use in the analyses by assigning a score of 1 to each item and summing the scores. The mean inter-item correlation for the total involvement scale was optimal (0.32).

6.4.2.9 School readiness. School readiness was assessed at age 4.5 years using direct measures and caregiver reports of child functioning across five neurodevelopmental domains: physical well-being and development, social-emotional skills, approaches to learning, language, and general cognitive development. *Physical well-being and visual-motor development* measures included a direct measure of visual-motor skills using the Beery-Buktenia Developmental Test of Visual-Motor Integration – 5th Edition (Beery-VMI), which has high internal consistency reliability and proven validity (Beery & Beery, 2006). Caregiver reports of child toilet training and oral health were also collected. *Social-emotional skills* were assessed using the 25-item caregiver-completed Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). This scale assessed child emotional, conduct, inattention/hyperactivity and peer relationship difficulties. A total difficulties score was calculated by summing scores across these four subscales. The SDQ is a well-validated screening measure for emotional and behavioural maladjustment, with good test-retest reliabilities for the total difficulties score (Goodman, 2001; Stone et al., 2010).

Approaches to learning was assessed using the Phelps Kindergarten Readiness Scale II (PKRS-II; Phelps, 2003). This assessed verbal, perceptual and auditory information processing skills. The PKRS-II has been validated as predictive of later child school achievement, and thus can be effective in identifying pre-school children with processing difficulties at risk of later educational delay (Augustyniak, Cook-Cottone, & Calabrese, 2004; Duncan et al., 2007). *Language development* was assessed using six subtests of the Clinical Evaluation of Language Fundamentals – Preschool (CELF-P; Wiig, Secord, & Semel, 1992). Subtests measuring receptive and expressive language development were administered to obtain a total language score. The CELF-P has been well-established as a reliable and valid measure of child language skills prior to school entry with good internal consistency and test-retest reliability (Morrow et al., 2004). Finally, *cognition and general knowledge* was

assessed using a short form of the Wechsler Preschool and Primary Scales of Intelligence – Revised (WPPSI-R; Wechsler, 1989). This consisted of two performance (Block Design and Picture Completion) and two verbal (Arithmetic and Comprehension) subtests. Scores from the short form of the WPPSI-R correlate highly ($r = .92$) with full-scale IQ scores (LoBello, 1991).

As described previously by Lee et al. (*in preparation*), children's total school readiness scores were calculated by creating cut-points for delay or impairment within each domain. Cut-points were chosen to allow for the comparability of base rates of delay across previous studies (Pritchard et al., 2014; Roberts et al., 2011), and to provide a conservative estimate of children's overall school readiness impairment. Delayed physical development was indicated by either a Beery-VMI standard score < 10th percentile of the score distribution of the non-ME group, a parent report of the child wetting or soiling their pants most days (Carr, 2003), or any tooth extractions due to decay by age 4.5 years (Blumenshine, Vann, Gizlice, & Lee, 2008). Social-emotional difficulty was indicated by a total SDQ difficulties score > 90th percentile of the non-ME group score distribution. Approaches to learning difficulty, language delay, and general cognitive delay were indicated by scores that were < 10th percentile of the non-ME group score distribution for the total PKRS-II, total CELF-P, and full WPPSI-R IQ scores, respectively. A child's total readiness score, the total number of domains in which they showed delay/impairment, was used in the analyses. Children with a greater number of domain delays were considered to have lower school readiness. The mean inter-item correlation for the total school readiness scale was good (.40).

6.5 Data Management and Analysis

6.5.1 Data entry. The author entered data from the 9-year standardised measures and teacher questionnaires into the wider longitudinal MIP study database. A post-graduate

psychology student cross-checked 10% of these data with the original paper files for imputing errors. Data were then exported into a file using the Statistical Package for the Social Sciences (SPSS) 22 (IBM Corp, Released 2013). A further 10% of the data were then checked for imputing accuracy. Additional data from previous follow-up waves were obtained from the existing MIP study databases, exported to SPSS, and subsequently cleaned and cross-checked by the author.

6.5.2 Effect sizes and statistical power. The Exploratory Software for Confidence Intervals (ESCI; Cumming, 2012) was used to calculate the effect sizes (Cohen's d) and their 95% confidence intervals for the between-group differences on continuous variables. Cohen's d for the magnitude of difference was interpreted as small ($d = 0.2$), medium ($d = 0.5$), or large ($d = 0.8$; Cohen, 1988). Effect sizes for dichotomous variables were presented as odds ratios (ORs). An OR "represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure" (Szumilas, 2010, p. 227). In logistic regression analyses the OR is used to represent "the change in odds of being in one of the categories of outcome when the value of a predictor increases by one unit" (Tabachnik & Fidell, 2014, p. 507). Effect sizes for the between-group differences in adjusted means were presented as partial eta squared (η_p^2). Following Cohen's (1998) guidelines, η_p^2 for the magnitude of difference was interpreted as small ($\eta_p^2 = 0.01$), medium ($\eta_p^2 = 0.09$), or large ($\eta_p^2 = 0.25$).

Post-hoc power analyses for univariate tests were performed using G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007). With two groups of size $N = 62$ and $N = 72$, power to detect a medium effect size ($d = .50$) at a significance level of $p < .05$ was 89%. There was 93% power to detect a medium effect size ($w = .30$) for chi-squared tests with 1 degree of freedom, and 88% power for chi-squared tests with 2 degrees of freedom.

6.5.3 Statistical methods. Data were analysed in three stages. Data were first explored to identify outliers or missing cases and to examine data distributions for each group. This included use of frequency tables, histograms, box plots and scatter plots. Descriptive statistics were then completed for dependent measures and included independent samples *t*-tests for continuous variables, and chi-square tests of independence for categorical variables. Statistical significance on these tests was set to $p < .05$. In the next stage, logistic regression was performed to examine the extent to which educational delay at age 9 years was associated with prenatal methadone exposure and/or associated infant clinical and maternal psychosocial risk factors. Potentially intervening caregiving variables were then added to the regression model to assess their association with educational delay at 9 years. Bootstrapping was used to determine whether there were specific, significant intervening factors between prenatal methadone exposure and educational delay. These latter two steps were repeated to examine the effect of children's level of school readiness at age 4.5 years on their educational outcome at age 9 years.

CHAPTER 7

Results 1: Methadone-exposed Children's Educational Outcomes

The first aim of this study was to describe the educational outcomes of a NZ cohort of children born to mothers enrolled in MMT during pregnancy in relation to their non-ME peers at age 9 years. To address this aim, this chapter provides a series of analyses comparing the ME and non-ME comparison groups on the standardised WJ-III Tests of Achievement. Children's performance on the WJ-III was also used to determine their rates of educational delay, and to examine the severity and specificity of those delays. Following this is a description of children's teacher-rated achievement across the NZ curriculum and their special education enrolment. Independent-samples *t*-tests and chi-square tests for independence were used to examine between-group differences on these outcomes.

The second aim was to examine the extent to which the between-group differences in children's educational outcomes reflected the direct effects of prenatal methadone exposure following adjustment for confounding factors. The potential confounders examined included maternal social background risks, other prenatal drug exposures, and infant clinical risks. Logistic regression analyses were performed to identify confounders significantly associated with educational delay. Finally an analysis of covariance was performed to examine children's mean achievement scores following adjustment for significant confounders.

7.1 Standardised Achievement Test Performance

Complete WJ-III data were available for all but two ME children. One of these children was too low functioning to complete the assessment at all, and one found two mathematics subtests very difficult and refused to complete them. There were also two ME

children with very low outlying scores on some subtests (< 30). The child that was too low functioning to complete the WJ-III was assigned a standard score of 40 for each WJ-III subtest and composite score. The child with two missing subtest scores was assigned the mean of their other completed subtests. The two children with very low outlying scores were assigned standard scores of 45. Assigning low functioning children the lowest possible test scores is a procedure that has been previously used in studies of vulnerable populations. This procedure reduces the impact of outliers on the WJ-III results, and by representing achievement for as many study children as possible the means more accurately reflect the outcomes of the cohort as a whole (Orchinik et al., 2011; Pritchard et al., 2009; Tabachnik & Fidell, 2014). Between-group comparisons were performed both including and excluding children identified as outliers in the data exploration phase of the analyses. Inclusion of these children's scores did not substantially alter the results, therefore they were included in the final analyses.

Large between-group differences were found on each reading subtest (d s, 0.71 – 1.00, Table 7.1). Specifically, ME children scored below non-ME children by 16.4 standard points for Letter-word Identification, 12.5 points for Reading Fluency, and 12.1 points for Passage Comprehension (p s $<.001$). Methadone-exposed children's mean Broad Reading score, indicating overall reading achievement from these three subtests, was close to 1 SD below the non-ME children's score ($d = 0.97$). Predominantly large between-group differences were also found on each mathematics subtest (d s, 0.67 – 1.06, Table 7.1). Methadone-exposed children scored below non-ME children by 15.7 standard points for Calculation, 10 points for Math Fluency, and 13.1 points for Applied Problem Solving (p s $<.001$). Methadone-exposed children's mean Broad Math score was close to 1 SD below the non-ME children's score ($d = 0.99$).

Table 7.1

Methadone-exposed and Comparison Children's Mean Performance on the WJ-III

WJ-III subtest	Methadone (N = 62)	Comparison (N = 72)	t	p	d (95% CI)
<i>M (SD)</i> Letter-word Identification	91.34 (18.94)	107.76 (14.06)	-5.72	<.001	1.00 (0.63 – 1.35)
<i>M (SD)</i> Reading Fluency	87.84 (18.65)	100.35 (16.43)	-4.11	<.001	0.71 (0.36 – 1.07)
<i>M (SD)</i> Passage Comprehension	86.92 (14.89)	99.04 (9.75)	-5.47	<.001	0.98 (0.62 – 1.34)
<i>M (SD) Broad Reading</i>	87.26 (19.29)	103.54 (14.35)	-5.47	<.001	0.97 (0.61 – 1.33)
<i>M (SD)</i> Calculation	82.16 (15.68)	97.87 (13.73)	-6.16	<.001	1.07 (0.71 – 1.43)
<i>M (SD)</i> Math Fluency	87.08 (14.67)	97.13 (15.39)	-3.84	<.001	0.67 (0.32 – 1.02)
<i>M (SD)</i> Applied Problem Solving	93.58 (16.02)	106.65 (11.91)	-5.27	<.001	0.94 (0.57 – 1.29)
<i>M (SD) Broad Math</i>	87.00 (16.66)	102.71 (15.02)	-5.74	<.001	0.99 (0.63 – 1.35)

Note. *d* = Cohen's *d* effect size; CI = confidence interval.

Children's educational delay was then determined using a cut-off score > 1 SD below the non-ME group mean on Broad Reading or Broad Math (Table 7.2). This identified children with at least a 12-month delay relative to their regionally representative peers (Taylor, 2000). Methadone-exposed children's risk for having a reading delay was 4 times greater than non-ME children's, with 40% compared with 10% scoring below this cut-off ($OR = 6.3, p < .001$). Methadone-exposed children's risk for having a mathematics delay was 7 times greater than non-ME children's, with 48% compared with 7% scoring below this cut-off ($OR = 12.6, p < .001$). Finally, ME children's risk for having any educational delay was 4.5 times greater than non-ME children's, with 57% vs. 13% having a reading or mathematics delay, or both ($OR = 9.1, p < .001$).

Table 7.2

Methadone-exposed Children's Odds of Reading and/or Mathematics Delay

	Methadone	Comparison			
	(N = 62)	(N = 72)	χ^2	<i>p</i>	OR (95% CI)
% reading delay	40.3	9.7	17.16	<.001	6.27 (2.48 – 15.91)
% mathematics delay	48.4	6.9	29.65	<.001	12.56 (4.46 – 35.41)
% any educational delay	56.5	12.5	29.18	<.001	9.07 (3.84 – 21.45)

Note. OR = odds ratio; CI = confidence interval.

Rates of specific learning disability were then determined by examining rates of children with educational delay, excluding those with severe intellectual impairment. Severe intellectual impairment was indicated by an IQ score > 2 SDs below the non-ME group's mean IQ score (< 78). Nine ME children and one non-ME child had severe intellectual impairment, leaving 53 ME children and 71 non-ME children eligible for inclusion in this analysis (see Table 7.3). Methadone-exposed children's risk for having a reading specific learning disability was 3 times greater than non-ME children's, with 30% vs. 10% meeting the low achievement criterion ($OR = 3.9, p = .002$). Methadone-exposed children's risk for having a mathematics specific learning disability was 5.7 times greater than non-ME children's, with 39% vs. 7% meeting the criterion ($OR = 8.7, p < .001$). Finally, ME children's risk for having any specific learning disability was 3.9 times greater than non-ME children's with 49% vs. 13% having a learning disability in one or both domains ($OR = 6.6, p < .001$).

Table 7.3

Methadone-exposed Children's Odds of Reading and/or Mathematics Specific Learning Disability

	Methadone	Comparison			
	(n = 53)	(n = 71)	χ^2	<i>p</i>	OR (95% CI)
% reading SLD	30.2	9.9	8.30	.004	3.95 (1.49 – 10.49)
% mathematics SLD	39.6	7.0	19.44	<.001	8.66 (2.99 – 25.07)
% any SLD	49.1	12.7	19.83	<.001	6.63 (2.75 – 16.03)

Note. SLD = specific learning disability; OR = odds ratio; CI = confidence interval.

7.2 Educational Delay Severity and Specificity

The next set of analyses was performed to describe ME and non-ME children's educational delay in more detail using the WJ-III Broad Reading and Broad Math total and subtest scores. Children's reading and mathematics delay severity was examined first. A mild delay was classified as a WJ-III Broad Reading or Math score between 1 and 2 SDs below the non-ME group mean. A severe delay was classified as a score > 2 SDs below the non-ME group mean. These cut-offs were used to indicate children with at least a 12-month, and at least a 24-month delay, respectively, compared to their regionally-representative peers. As shown in Figure 7.1, ME children had significantly higher rates of both mild (19% vs. 6%) and severe reading delay (21% vs. 4%, $\chi^2 = 17.29, p < .001$) than non-ME children. They also had significantly higher rates of mild (30% vs. 3%) and severe mathematics delay (18% vs. 4%, $\chi^2 = 29.39, p < .001$).

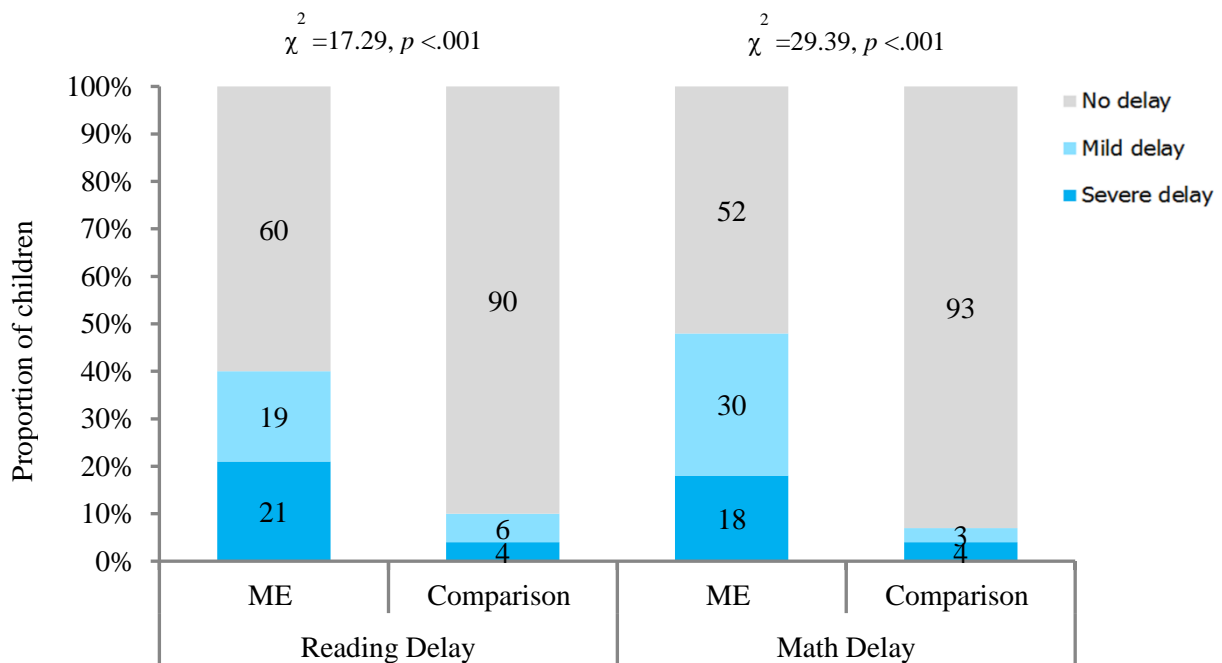


Figure 7.1. Rates of mild and severe educational delay amongst methadone-exposed and comparison children.

Patterns of reading and mathematics comorbidity among ME and non-ME children with an educational delay were examined next. Large proportions of ME children with one delay had a co-occurring delay. More than half of the delayed ME children had reading and mathematics comorbidity, whereas one third of the delayed non-ME children had reading and mathematics comorbidity ($\chi^2_{\text{linear trend}} = 28.93, p < .001$, Figure 7.2).

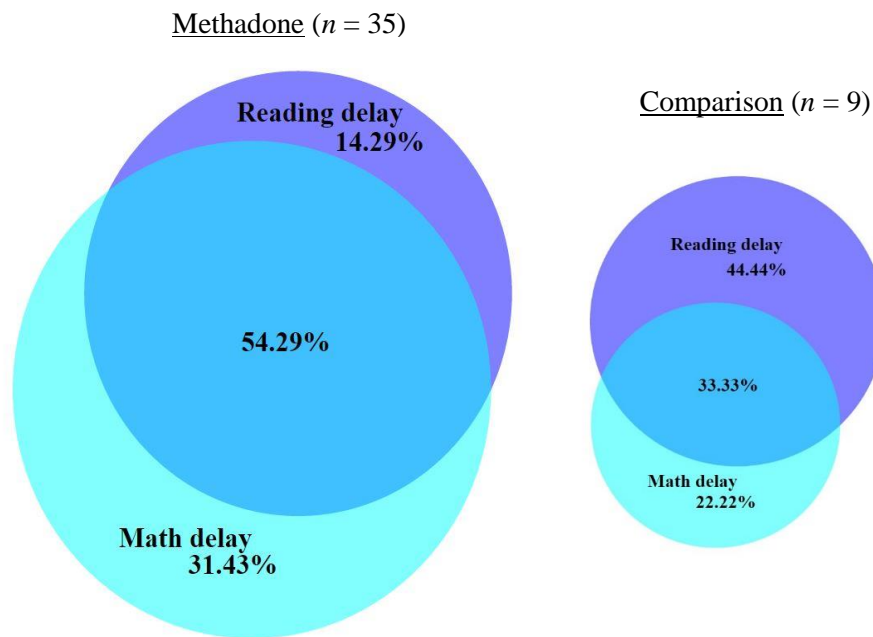


Figure 7.2. Patterns of educational comorbidity amongst methadone-exposed and comparison children.

The WJ-III scores of the subgroup of ME children identified as having reading and mathematics delays were then examined to assess the specific academic skills that were impaired for these children (Table 7.4). No particular reading skill was more impaired than others among the ME children with a reading delay ($n = 25$). Their mean Letter-word Identification and Passage Comprehension scores were > 2 SDs below, and their mean reading Fluency score was close to 1.5 SDs below the non-ME group mean scores recorded above. Methadone-exposed children with a mathematics delay ($n = 29$) showed the most impaired performance on the Calculation subtest, followed by Math Fluency and then

Applied Problem Solving. Their mean score on the Calculation subtest was >2 SDs below, whereas their mean Math Fluency and Applied Problem Solving scores were within 1.5 SDs of the non-ME group's mean scores.

Table 7.4

Mean WJ-III Reading and Mathematics Subtest Scores of Methadone-exposed Children with Educational Delay

Reading-delayed children	
WJ-III reading subtest	(<i>n</i> = 25)
<i>M (SD)</i> Letter-word Identification	73.44 (14.76)
<i>M (SD)</i> Reading Fluency	71.36 (16.72)
<i>M (SD)</i> Passage Comprehension	74.56 (15.43)
Math-delayed children	
WJ-III mathematics subtest	(<i>n</i> = 29)
<i>M (SD)</i> Calculation	70.45 (13.42)
<i>M (SD)</i> Math Fluency	76.38 (12.09)
<i>M (SD)</i> Applied Problem Solving	82.38 (15.02)

7.3 Teacher Ratings of Children's Achievement

School achievement data were available for all 134 children. At age 9 years, 94% of ME children and 100% of non-ME comparison children attended a mainstream primary school. Of the ME children that were not enrolled at mainstream schools ($n = 4$), one attended a state special education school for children with very high needs, one attended a private school for children with severe learning difficulties, one attended a state special character school focussing on self-led learning and social-emotional skill development, and one had been recently expelled from school due to severe behaviour problems. School performance data for the latter child was obtained from their previous classroom teacher.

The ME group was characterised by significantly poorer school performance than the non-ME group across all curriculum domains, except physical education. Relative risks

across subjects ranged from 1.5 to 3.2, and ORs ranged from 1.7 to 6.4 (Table 7.5). The most frequently reported problem was in the domain of written language, with 65% of ME compared with 22% of non-ME children rated as below average to more than 12-months delayed ($OR = 6.4$; $p < .001$). The next most common domains of difficulty were reading and mathematics, with 55% and 53% of ME children, respectively, compared to 17% of non-ME children rated as below average to more than 12-months delayed (ORs , 6.1 and 5.7; $ps < .001$). Methadone-exposed children also had increased odds for below average/delayed performance in expressive language ($OR = 4.1$, $p = .002$), art ($OR = 2.5$; $p = .03$), health ($OR = 4.5$, $p = .002$), and technology ($OR = 3.2$; $p = .01$). Within the ME group, 79% ($n = 49$) were rated as below average or delayed in one or more academic skill areas, and 52% ($n = 32$) were below average or delayed in three or more areas.

Table 7.5

Methadone-exposed and Comparison Children's Teacher-Rated School Performance

Curriculum domain	Methadone (<i>N</i> = 62)	Comparison (<i>N</i> = 72)	χ^2	<i>p</i>	<i>OR</i> (95% <i>CI</i>)
% below average/delayed reading	54.8	16.7	21.53	<.001	6.07 (2.74 – 13.46)
% below average/delayed math	53.2	16.7	19.96	<.001	5.69 (2.57 – 12.61)
% below average/delayed written language	64.5	22.2	24.50	<.001	6.36 (2.97 – 13.62)
% below average/delayed expressive language	30.6	9.7	9.33	.002	4.10 (1.59 – 10.59)
% below average/ delayed art	29.0	13.9	4.62	.03	2.54 (1.07 – 6.02)
% below average/delayed physical education	25.8	16.7	1.68	.19	1.74 (0.75 – 4.03)
% below average/delayed health	29.0	8.3	9.71	.002	4.50 (1.66 – 12.23)
% below average/delayed technology	25.8	9.7	6.06	.01	3.23 (1.23 – 8.48)

Note. *OR* = odds ratio; *CI* = confidence interval.

7.4 Special Education

A larger proportion of ME than non-ME children were receiving special education at school (37.1% vs. 9.7%, $p < .001$, see Table 7.6). This included higher rates of ME than non-ME children with special education support from their individual schools (24% vs. 8%, $p = .01$), and from their region's RTLBs (6.5% vs. 1.4%, $p = .12$). Further, 6.5% of ME children had ORS funding, and 3.2% of ME children were in the process of applying for ORS funding. These ORS-funded children represented those with one or more neurodevelopmental disabilities, including severe intellectual impairment, severe reading and/or mathematics delay, perceptual-motor problems or other severe health and development problems. None of the non-ME comparison children were eligible for ORS funding.

Table 7.6

Methadone-exposed and Comparison Children's Special Education Support at School

Type of educational support service	Methadone	Comparison	χ^2	p
	($N = 62$)	($N = 72$)		
% any support service	37.1	9.7	14.4	<.001
% school-funded teacher aide	24.2	8.3	6.34	.01
% RTLB	6.5	1.4	2.37	.12
% ORS	6.5			
% awaiting ORS funding	3.2			

Note. RTLB = Resource Teachers of Learning and Behaviour; ORS = Ongoing Resourcing Scheme.

Table 7.7 shows a more detailed examination of the special education support received by the ME and non-ME children who were identified as having any educational delay on the WJ-III. Just over half of the ME (57%) and non-ME (56%) children with an educational delay were receiving special education support at school. Therefore, over two fifths of the delayed children in each group had no school-based learning support. The types of services received by educationally-delayed children included individual or group-based

teacher aide assistance in the classroom (51% vs. 56%, $p = .93$), followed by literacy programmes (22.9% vs. 33.3%, $p = .52$), behaviour management programmes (17.1% vs. 11.1%, $p = .66$), and perceptual motor programmes (5.7% vs. 11.1%, $p = .57$). Further, 20% of the ME children were enrolled in a social skills programme, 5.7% were enrolled in occupational therapy/physiotherapy, and 5.7% were enrolled in speech and language therapy.

Table 7.7

Educational Support Services at School of Methadone-exposed and Comparison Children with an Educational Delay on the WJ-III

Types of educational support service	Methadone	Comparison	χ^2	p
	($n = 35$)	($n = 9$)		
% any support service	57.1	55.6	.01	.93
% any teacher aide	51.4	55.6	.05	.83
% literacy	22.9	33.3	.42	.52
% behaviour management	17.1	11.1	.20	.66
% perceptual motor	5.7	11.1	.33	.57
% social skills	20.0			
% occupational therapy	5.7			
% speech and language	5.7			
Range, total number of support services	0 – 6	0 – 3		

7.5 Prenatal Methadone Exposure and Risk for 9-year Educational Delay Following Adjustment for Confounding Factors

The bivariate analyses performed thus far indicated that ME children had poorer educational outcomes relative to their non-ME peers. However, as shown in Table 6.4 (Chapter 6, page 78), and as identified in previous research, women enrolled in MMT during pregnancy are commonly characterised by high levels of psychosocial disadvantage, and are likely to continue using licit and illicit drugs during pregnancy. Additionally, their children are more likely than non-ME children to have been born preterm or small for gestational age.

It is therefore possible that these associated risk factors confounded the association between prenatal methadone exposure and 9-year educational delay.

The aim of the next stage of analysis was therefore to assess the extent to which prenatal methadone exposure predicted having an educational delay following adjustment for the potentially confounding effects of maternal psychosocial and infant clinical factors. A number of steps were taken to identify a regression model comprised of the most stable set of predictors correctly classifying children with any educational delay as opposed to no delay. This dichotomous outcome variable was used given that the majority of delayed ME children showed both reading and mathematics delay. Further, using the outcome *any delay* is useful in determining the extent to which prenatal methadone exposure and/or confounders are related to children achieving more than 12 months behind their same-age peers, which is one of the eligibility criteria for receiving special education within NZ schools. Additionally, separate linear regression analyses that examined the confounding factors associated with the separate continuous reading and mathematics scores revealed results similar to those shown below.

7.5.1 Identifying confounders. A confounder was initially selected for use in the regression model if: (a) there was a significant between-group difference on that variable indicating its association with maternal enrolment in MMT during pregnancy, and/or (b) previous research and theory linked the confounder to children's educational outcomes. The maternal social background characteristics considered included SES, educational attainment, partner status, ethnicity, and age at delivery. Poly-drug use during pregnancy was also taken into consideration. Infant clinical variables considered included sex, gestational age, birth weight, length, and head circumference. Gestational age was included as a covariate despite the exclusion of children born < 33 weeks from the study, and that there were no between-

group differences in gestational age. Late preterm born children (33 to 37 weeks gestation) were included in the study, however.

The association between each of the variables associated with maternal MMT enrolment and educational delay was assessed using bivariate *t*-tests and chi-square tests of independence. Variables that were not significantly associated with educational delay were not considered for use in the regression models. A conservative cut-off of $p < .10$ was used to indicate a significant association rather than $p < .05$, given the size of the sample.

Associations between the potential confounders were also examined. Maternal education level and family SES were highly correlated ($r = .75$). Consideration was given to including SES and maternal education in the regression analyses within a composite measure of social risk that also comprised young motherhood, minority ethnicity and single parenthood. However, following preliminary analyses using both this cumulative social risk index and its component variables, maternal educational attainment at birth was decided upon as the sole social risk indicator for the remaining covariate analyses. This decision was further justified on the basis that previous research has linked maternal education level and children's educational and other cognitive outcomes in the literature (Caro et al., 2009; Konijnenberg & Melinder, 2015; Messinger et al., 2004; Oei et al., 2017; Perry & Fantuzzo, 2010).

7.5.2 Regression summary. Methadone group status and significant associated confounders were entered as independent variables in a series of logistic regression analyses using forwards, backwards and sequential methods. A significance level of $p < .10$ was used to determine whether to include a particular independent variable in the model at each step. The results of the regression analyses are summarised in Table 7.8. Two covariates were significantly associated with children's risk of having an educational delay. These were maternal educational attainment ($p = .01$), and gestational age ($p = .01$). Although the association between prenatal methadone exposure and having an educational delay was

attenuated following adjustment for these confounding factors, methadone group status remained significantly associated with educational delay ($p = .02$). The final model including confounders was statistically significant, $\chi^2(3, N = 134) = 44.93, p < .001$, and as a whole explained between 28.5% (Cox and Snell R^2) and 39.7% (Nagelkerke R^2) of the variance in educational delay status. The model correctly identified 76.1% of children with any educational delay. Other confounders including child sex, birth parameters, extent of prenatal poly-drug exposure, and other maternal social risk indicators (single parenthood, low SES, ethnic minority status, young motherhood) did not uniquely contribute to the model.

Table 7.8 also shows the unstandardized regression coefficient (B) and standard error (SE) of B , Wald statistics, ORs and 95% confidence intervals for the ORs, for each of the covariates in the final model. Positive B values indicate that an increase in the independent variable score will result in an increased probability of the child being categorised as having educational delay. Negative B values indicate that an increase in the independent variable score will result in a decreased probability of the child being categorised as having educational delay. The Wald test and the statistical significance of this test (p) indicate whether the independent variable uniquely contributes to the predictive ability of the regression model for identifying children with educational delay. Finally the OR indicates the change in a child's odds of having an educational delay with every unit increase in a particular independent variable. If the 95% confidence interval of the OR does not include zero, the variable can be interpreted as uniquely predicting educational delay.

Methadone group status, maternal educational attainment, and gestational age each made a unique, statistically significant contribution to the model. Children's group status showed the largest effect size, with ME children's odds for educational delay 3.6 times greater than non-ME children's, controlling for maternal education and gestational age ($OR = 3.64, p = .02$). Children's odds for educational delay were decreased by 38% for every

additional educational qualification held by their mothers at birth ($OR = 0.62, p = .01$), and were decreased by 30% for every additional week of gestation ($OR = 0.70, p = .01$). Two- and three-way interactions between the covariates were examined by creating multiplicative terms and entering these in the regression model. There were no significant interaction effects between group, maternal education and gestational age and their association with educational delay.

Table 7.8

Summary of Logistic Regression Analysis for Confounding Factors Associated with Educational Delay (0 = no delay, 1 = delay)

Variable	<i>B</i> (<i>SE</i>)	Wald	<i>p</i>	<i>OR</i> (95% <i>CI</i>)
Step 1. Unadjusted				
Prenatal methadone exposure	2.21 (.44)	24.86	<.001	9.07 (3.84 – 21.45)
Step 2. Adjusted for confounding factors				
Prenatal methadone exposure	1.29 (.55)	5.53	.02	3.64 (1.24 – 10.71)
Maternal educational attainment	-0.48 (.19)	6.07	.01	0.62 (0.24 – 0.91)
Gestational age	-0.36 (.14)	6.43	.01	0.70 (0.53 – 0.92)

Note. *OR* = odds ratio; *CI* = confidence interval.

A one-way analysis of covariance was then performed to assess the between-group differences in children's mean Broad Reading and Math scores following adjustment for maternal education level and infant gestational age (see Table 7.9). A moderate, significant difference in Broad Reading scores remained following covariate adjustment, $F(1, 129) = 8.08, p = .005, \eta_p^2 = .06$. There was a smaller, yet statistically significant difference in Broad Math scores following covariate adjustment, $F(1, 130) = 4.06, p < .047, \eta_p^2 = .03$. An interaction effect between group status and gestational age for both the continuous Broad Reading and Broad Math outcome scores was also found ($ps = .04$; see Figure 7.3), indicating that ME children who were born at a lower gestational age had lower reading and mathematics test scores than ME children born at a higher gestational age.

Table 7.9

Adjusted Group Means for WJ-III Tests of Achievement Scores

WJ-III cluster	Methadone (N = 62)	Comparison (N = 72)	p	η^2
<i>M (SE)</i> Broad Reading	90.27 (2.42)	100.95 (2.24)	.005	.06
<i>M (SE)</i> Broad Math	91.83 (2.30)	98.84 (2.07)	.046	.03

Note. Means adjusted for infant gestational age and maternal educational attainment at birth.

7.6 Chapter Summary

Methadone-exposed children had significantly lower mean scores than their non-ME comparison peers on standardised tests of reading and mathematics achievement. As a group, the ME children were characterised by higher rates of reading and mathematics delay and specific learning disability. An examination of the specific skills of the subgroup of educationally-delayed children showed there was no particular reading subtest in which ME children were more impaired in than others. The children with a mathematics delay showed most impaired performance in the Calculation subtest. In addition to lower standardised reading and mathematics test scores, ME children had lower teacher-rated school performance across the curriculum, and were more likely to be receiving special educational support at school. Results from logistic regression analyses showed that maternal educational attainment and gestational age attenuated the association between prenatal methadone exposure and educational delay. Nonetheless the link between prenatal exposure and educational delay could not be fully explained by these confounding factors. The following chapter examines possible factors that may assist in explaining this association.

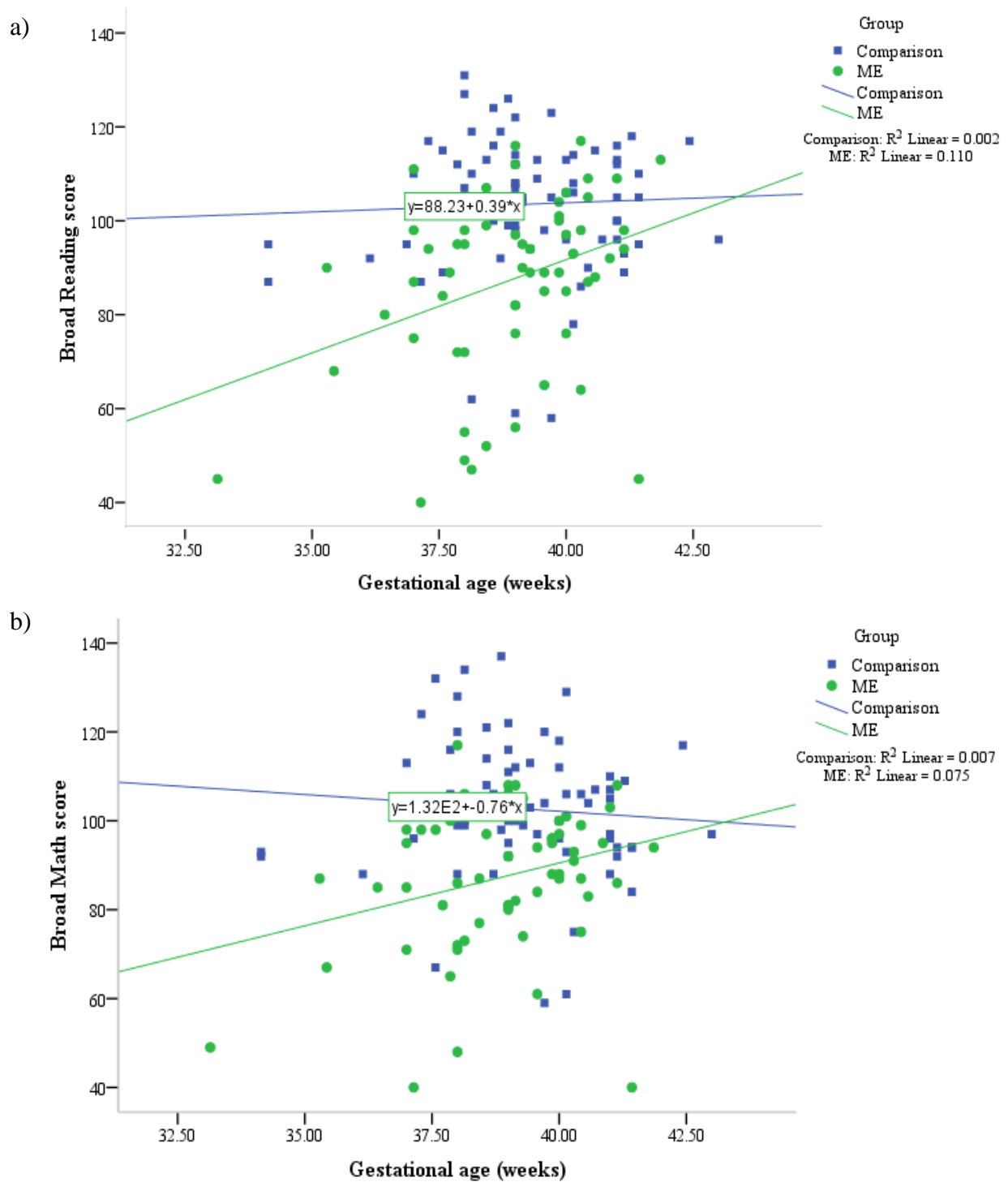


Figure 7.3. Methadone exposure and gestational age interaction effects on WJ-III scores

CHAPTER 8

Results 2: The Role of the Caregiving Environment in the Association between Prenatal Methadone Exposure and 9-year Educational Delay

The final aim of this study was to assess whether ME and non-ME children differ on a range of caregiving factors from birth up to 9 years, and whether between-group differences in caregiving factors, in turn, predict differences in children's educational outcomes. To address this aim, this chapter provides a description of the family environments in which ME and non-ME children were raised. Independent-samples *t*-tests and chi-square tests for independence were used to examine between-group differences on these outcomes. Logistic regression analyses were then performed to identify intervening variables significantly associated with having an educational delay. Finally, bootstrapping was performed to assess the direct and indirect effects of children's prenatal methadone exposure on their risk for having an educational delay in a model including those significant intervening variables.

8.1 Caregiving Characteristics and Family Environment across Childhood

A number of variables were chosen as reflective of the children's caregiving experiences in the intervening years between prenatal methadone exposure and the developmental assessment at age 9 years. These were the frequency of children's primary caregiver changes, their caregiver's ongoing illicit drug use and psychological well-being, the quality of their early home environments, and their caregiver's school involvement at age 9 years. Data from the 18-month, 2-year, 4.5-year and 9-year follow-ups were available for all 134 children in the current study.

8.1.1 Primary caregiver changes. Children's primary caregiver changes were recorded at each assessment follow-up. Although there were some parental separations in the

non-ME comparison group, the non-ME children had no changes in their primary caregiver status at any age. The following data (Table 8.1) are therefore presented for the ME group only. At the first study follow-up at age 18 months, close to 18% of ME children had experienced at least one primary caregiver change. This increased to 26% at age 2 years, 36% at age 4.5 years, and 59% at age 9 years. Methadone-exposed children experienced between zero and seven changes in primary caregiver from birth to 9 years.

Table 8.1

Methadone-exposed Children's Primary Caregiver Changes from Birth to 9 Years

Follow-up	Cumulative % with any primary caregiver change	Range in total number of primary caregiver changes
18 months	17.7	0 – 3
2 years	26.2	0 – 3
4.5 years	36.1	0 – 4
9 years	59.0	0 – 7

8.1.2 Caregivers' ongoing illicit substance use. As shown in Table 8.2, over one third of ME children's caregivers reported illicit substance use at 18 months, 4.5 years and 9 years. Nearly two thirds (63%) of ME children had a substance-using caregiver during their childhood, compared to 6% of non-ME children. Cannabis was the predominant substance that methadone group caregivers reported using across ages. This was followed by sedative (18%), stimulant (8%) and illicit opioid use (7%). These caregivers were more likely to use multiple illicit substances compared to comparison caregivers, using up to four different substances ($M = 1.31$, $SD = 1.36$), compared to a maximum of one substance ($M = 0.06$, $SD = 0.23$) respectively, between the 18-month and 9-year follow-up.

Table 8.2

Primary Caregiver Illicit Drug Use to Age 9 Years

Illicit drug use at each follow-up	Methadone (N = 62)	Comparison (N = 72)	χ^2	<i>p</i>	<i>d</i>
% any illicit drug use at 18 months	37.1	2.8	25.85	<.001	
% any illicit drug use at 4.5 years	33.9	0.0	-	-	
% any illicit drug use at 9 years	37.1	2.8	25.85	<.001	
Total illicit drug use					
% any illicit drug use from 18 months to 9 years	62.9	5.6	50.58	<.001	
<i>M (SD)</i> poly-drug use score from 18 months to 9 years	1.31 (1.36)	0.06 (0.23)	7.33	<.001	1.28

8.1.3 Caregiver depression scores. Methadone-exposed children had higher

caregiver depression scores than non-ME children at birth, 18 months, 4.5 years and 9 years of age (*ds*, 0.92 – 1.20, see Table 8.3). Methadone-exposed children therefore had increased exposure to caregiver depressive symptomology from birth to 9 years, with a cumulative mean score that was 1.5 SDs above the non-ME children's mean score.

Table 8.3

Primary Caregiver Depression Scores to Age 9 Years

Depression scores at each follow-up	Methadone (N = 62)	Comparison (N = 72)	<i>t</i>	<i>p</i>	<i>d</i>
<i>M (SD)</i> maternal depression score, birth	11.47 (6.42)	5.15 (4.69)	6.40	<.001	1.12
<i>M (SD)</i> caregiver depression score, 18 months	10.56 (7.42)	4.81 (3.98)	5.47	<.001	0.97
<i>M (SD)</i> caregiver depression score, 4.5 years	6.81 (4.94)	2.03 (2.73)	6.78	<.001	1.20
<i>M (SD)</i> caregiver depression score, 9 years	6.31 (4.88)	2.44 (3.42)	5.22	<.001	0.92
Total caregiver depression scores					
<i>M (SD)</i> cumulative caregiver depression score, birth to 9 years	35.15 (16.37)	14.45 (10.66)	8.52	<.001	1.50

Note. Depressive symptomology was measured using the Edinburgh Postnatal Depression Scale at birth and at 18 months, and was measured using the Composite International Diagnostic Interview at 4.5 and 9 years

8.1.4 The quality of the early caregiving environment. The HOME inventory was used at age 18 months to assess ME and non-ME children's early environmental stimulation, learning opportunities and parental support (Davie-Gray, 2011). The individual HOME subscale scores (see Table 8.4) indicated that ME children were more likely to be raised by parents with lower emotional and verbal responsiveness ($p = .04$), lower acceptance of sub-optimal child behaviour ($p = .01$), lower child involvement ($p < .001$), and who provided fewer opportunities for variety in daily stimulation ($p < .001$). There were no differences in how the ME and comparison group caregivers managed to organise the home environment ($p = .08$), or provide a range of play materials for their children ($p = .10$). A lower total HOME score for the ME relative to the non-ME group indicated that ME children were raised in overall lower quality environments ($p < .001$). Group differences on individual subscales and the Total HOME scored ranged from small to large in magnitude (ds , 0.30 – 1.01).

Table 8.4

Children's Mean 18-month HOME Scores

HOME subscale	Methadone	Comparison	<i>t</i>	<i>p</i>	<i>d</i>
	(<i>N</i> = 62)	(<i>N</i> = 72)			
<i>M</i> (<i>SD</i>) Responsivity of Parent	8.32 (2.14)	9.03 (1.82)	-2.06	.04	0.36
<i>M</i> (<i>SD</i>) Acceptance of Child Behavior	6.54 (1.35)	7.06 (1.01)	-2.50	.01	0.44
<i>M</i> (<i>SD</i>) Organisation of Physical and Temporal Environment	5.32 (0.81)	5.54 (0.69)	-1.74	.08	0.30
<i>M</i> (<i>SD</i>) Provision of Appropriate Play Materials	7.73 (1.33)	8.06 (0.89)	-1.66	.10	0.30
<i>M</i> (<i>SD</i>) Parental Involvement with Child	3.60 (1.96)	5.15 (1.29)	-5.32	<.001	0.95
<i>M</i> (<i>SD</i>) Opportunities for Variety in Daily Stimulation	3.65 (1.15)	4.56 (0.63)	-5.58	<.001	1.01
<i>M</i> (<i>SD</i>) Total HOME score	35.15 (5.95)	39.39 (3.87)	-4.81	<.001	0.86

Note. HOME = Home Observation for Measurement of the Environment.

8.1.5 Caregiver school involvement. According to teachers, a significantly smaller proportion of ME than non-ME children's caregivers were involved in their schooling. The ME group had caregivers who were less likely to assist teachers during in-class or out-of-class activities, to help with other school activities, and to attend parent-teacher meetings (Table 8.5). Methadone-exposed children's caregivers were involved in an average of 1.29 school-related activities, whereas comparison caregivers were involved in an average of 2.14 school-related activities ($d = 0.73$).

Table 8.5

Children's Primary Caregiver School Involvement

Involvement type	Methodone	Comparison	χ^2/t	<i>p</i>	<i>d</i>
	(<i>N</i> = 62)	(<i>N</i> = 72)			
% involved in help in class	6.6	23.6	7.22	.007	
% involved in help with out-of-class activities	29.5	58.3	11.08	.001	
% involved in other school activities	21.3	45.8	8.78	.003	
% attend parent-teacher sessions	70.5	86.1	4.85	.03	
<i>M</i> (<i>SD</i>) total involvement score	1.29 (1.06)	2.14 (1.25)	4.25	<.001	0.73

8.2 Children's Caregiving Factors and Educational Delay

As described in Chapter 7, prenatal methadone exposure was associated with educational delay after adjustment for maternal educational attainment at birth and gestational age. The aims of the following analyses were to assess whether persisting group differences in children's educational delay status were explained by the different caregiving environments in which ME and non-ME comparison children were raised over their 9 years of childhood.

The logistic regression model from Chapter 7 was extended to include intervening factors significantly ($p < .10$) associated with educational delay. Forwards and backwards variable elimination was first used to identify a parsimonious model. The results of the

regression analyses are summarised in Table 8.6. Three caregiving environment variables were significantly associated with educational delay (step 3). These were primary caregiver changes ($p = .03$), caregiver depression scores at 18 months ($p = .05$), and lower caregiver school involvement ($p = .01$). Caregiver illicit drug use, 18-month HOME scores, and caregiver depression scores at the other assessment follow-ups were not uniquely associated with educational delay.

Table 8.6

Summary of Logistic Regression Analysis for Confounding and Intervening Factors Associated with Educational Delay (0 = no delay, 1 = delay)

Variable	<i>B (S.E)</i>	Wald	<i>p</i>	<i>OR (95% CI)</i>
Step 1. Unadjusted				
Prenatal methadone exposure	2.19 (0.44)	24.86	<.001	9.07 (3.84 – 21.45)
Step 2. Adjusted for confounding factors				
Prenatal methadone exposure	1.29 (0.55)	5.55	.02	3.65 (1.24 – 10.72)
Maternal educational attainment	-0.48 (.19)	6.07	.01	0.62 (0.24 – 0.91)
Gestational age	-0.36 (.14)	6.43	.01	0.70 (0.53 – 0.92)
Step 3. Adjusted for confounding and environmental factors				
Prenatal methadone exposure	0.34 (0.67)	0.27	.61	1.41 (0.38 – 5.19)
Maternal educational attainment	-0.28 (0.20)	2.10	.15	0.75 (0.51 – 0.11)
Gestational age	-0.30 (0.15)	4.11	.04	0.74 (0.56 – 0.99)
Total primary caregiver changes to 9 years	0.62 (0.28)	4.99	.03	1.85 (1.08 – 3.17)
18-month caregiver depression score	0.08 (0.04)	3.83	.05	1.08 (1.00 – 1.17)
9-year caregiver school involvement score	-0.62 (0.25)	6.05	.01	0.54 (0.33 – 0.88)

Note. OR = odds ratio; CI = confidence interval.

The final model that included confounders and caregiving factors was statistically significant, $\chi^2(6, N = 134) = 62.10, p < .001$, and as a whole explained between 37% (Cox and Snell R^2) and 52% (Nagelkerke R^2) of the variance in educational delay status. The model correctly identified 82.8% of children with any educational delay at age 9 years. The unique

contributions of each significant intervening factor in the model are also shown in Table 8.6. Children's odds of having an educational delay were increased by 85% with every additional primary caregiver change they experienced from birth to age 9 years ($OR = 1.85, p = .03$), were increased by 8% with every 1-point increase on the caregiver-completed Edinburgh Postnatal Depression Scale at 18 months ($OR = 1.08, p = .05$), and were decreased by 46% with every additional school activity their caregiver was involved in at age 9 years ($OR = 0.54, p = .01$). Including these factors in the model attenuated the association between prenatal methadone exposure and 9-year educational delay ($OR = 1.41, p = .61$).

Bootstrapping was also used to quantify each of the intervening (indirect) effects and improve the Type I error control for testing the statistical significance of the mediator effects (Hayes, 2009; Preacher & Hayes, 2008). This method is recommended in addition to the causal steps approach and instead of the Sobel test. The causal steps approach is not based on the quantification of the intervening effect, rather the existence of an indirect effect is inferred based on whether its constituent paths are different from zero (Baron & Kenny, 1986). The Sobel Test, frequently used to supplement the causal steps approach, is also flawed. Unlike the Sobel Test, bootstrapping makes no assumptions about the normality of the sampling distribution of the indirect effect. Further, bootstrapping can be used to test multiple mediation models, where the total and direct effects of an independent variable on a dependent variable, as well as unique indirect intervening effects, are estimated (Hayes, 2009; Preacher & Hayes, 2008). An inference is made about the size of the indirect effect in the population using 5000 sample estimates to generate a bias-corrected (*BC*) 95% bootstrap confidence interval by sorting the 5000 paths' values from smallest to largest. If zero is not within the 95% confidence interval the indirect effect can be interpreted as significantly different from zero.

The PROCESS macro for SPSS (Hayes, 2013) was used to examine the change in the direct effect of methadone group status on educational delay after adjusting for the intervening factors using bootstrapping. The effects of the intervening factors in the association between prenatal methadone exposure and educational delay were estimated controlling for the effects of maternal educational attainment and infant gestational age. The bootstrapping analysis results (Table 8.7) indicated that caregiver changes (coefficient = 0.64, *BC* 95% *CI*, 0.15 – 1.34) and caregiver depression scores at 18 months (coefficient = 0.42, *BC* 95% *CI*, 0.04 – 1.02) were significant specific intervening factors. The combined indirect effect for caregiver changes and caregiver depression at 18 months was also significant (coefficient = 1.06, *BC* 95% *CI*, 0.39 – 1.88). Caregiver school involvement was not a significant intervening factor, with results indicating that the link between methadone group status and this variable was explained by the higher likelihood for ME children to be born to mothers with lower levels of education, and that mothers with lower levels of education were, in turn, less likely to be involved in their child’s schooling.

Table 8.7

The Intervening Role of Caregiving Factors in the Association between Prenatal Methadone Exposure and 9.5-year Educational Delay

Intervening process	Indirect effect	
	coefficient	<i>BC</i> 95% <i>CI</i>
Total indirect effect*	1.06	0.39 – 1.88
Total primary caregiver changes across childhood*	0.64	0.15 – 1.34
Caregiver depression score at 18 months*	0.42	0.04 – 1.02

Note. *BC* 95% *CI* = Bias-corrected 95% confidence interval of the indirect effect coefficient. Covariates entered: maternal education ($p = .03$), gestational age ($p = .02$).

* $p < .05$.

8.3 School Readiness and Educational Delay

Given the high rates of educational delay amongst the ME group in this study an additional set of analyses were undertaken. The following supplementary analyses examined the extent to which children at risk for educational delay could be identified prior to school entry, through their performance on a previous school readiness assessment at age 4.5 years.

Children's school readiness at age 4.5 years was measured using an assessment of their functioning across five neurodevelopmental domains (Lee et al., *in preparation*). These domains included physical well-being and visual-motor development, social-emotional skills, approaches to learning, language, and general cognitive development. A relatively low proportion of ME children were free of any school readiness domain delay at age 4.5 years (29% vs. 71%). These children were more likely to have multiple domains of delay, with 47% having delay in two or more domains compared with 13% of the non-ME children ($\chi^2_{\text{linear trend}} = 29.90, p < .001$, see Table 8.8). Methadone-exposed children had an average of 1.9 school readiness domain impairments compared to non-ME children who had an average of 0.5 school readiness domain impairments ($d = 0.98$).

Table 8.8

Number of School Readiness Domains Impaired at Age 4.5 Years

Number of domains impaired	Methadone	Comparison	χ^2/t	<i>p</i>	<i>d</i>
	(<i>N</i> = 62) %	(<i>N</i> = 72) %			
0	29.0	70.8			
1	24.2	16.7			
2	9.7	6.9			
3	11.3	1.4			
4	16.1	4.2			
5	9.7	0.0	29.90	<.001	
<i>M</i> (<i>SD</i>) total readiness score	1.90 (1.75)	0.51 (0.99)	-5.52	<.001	0.98

Note. Higher total readiness scores indicate lower school readiness.

Children's total school readiness score was added to the logistic regression model presented in the previous section, to examine the extent to which the total number of domain impairments children demonstrated at school entry predicted later educational delay (see Table 8.9). Children's odds of having an educational delay were increased by 65% with every additional domain of school readiness impairment observed at age 4.5 years ($OR = 1.65, p = .005$).

Table 8.9

Summary of Logistic Regression Analysis for 4.5-year School Readiness, Confounding, and Intervening Factors Associated with Educational Delay (0 = no delay, 1 = delay)

Variable	<i>B</i> (<i>S.E.</i>)	Wald	<i>p</i>	<i>OR</i> (95% <i>CI</i>)
Prenatal methadone exposure	-0.10 (0.74)	0.02	.89	0.91 (0.21 – 3.86)
Maternal educational attainment	-0.18 (0.21)	0.73	.39	0.84 (0.56 – 1.26)
Gestational age	-0.28 (0.17)	2.77	.10	0.76 (0.55 – 1.05)
Total primary caregiver changes to 9 years	0.67 (0.28)	5.58	.02	1.95 (1.12 – 3.41)
18-month caregiver depression score	0.09 (0.04)	4.77	.03	1.10 (1.01 – 1.20)
9-year caregiver school involvement score	-0.38 (0.27)	2.03	.15	0.69 (0.41 – 1.15)
4.5-year school readiness score	0.50 (0.18)	7.73	.005	1.65 (1.16 – 2.35)

Note. OR = odds ratio; CI = confidence interval.

Bootstrapping analysis also showed, controlling for confounders and caregiving factors, that children's school readiness score had a significant effect on educational outcome, with ME children demonstrating lower school readiness at age 4.5 years which, in turn, predicted educational delay at age 9 years (coefficient = 0.50, *BC* 95% *CI*, 0.03 – 1.25, see Table 8.10).

Table 8.10

The Intervening Role of School Readiness in the Association between Prenatal Methadone Exposure and 9.5-year Educational Delay

Intervening process	Indirect effect	
	coefficient	BC 95% CI
Total indirect effect*	1.75	0.72 – 2.92
Total primary caregiver changes across childhood*	0.75	0.17 – 1.55
Caregiver depression score at 18 months*	0.50	0.05 – 1.18
School readiness score*	0.50	0.05 – 1.26

Note. BC 95% CI = Bias-corrected 95% confidence interval of the indirect effect coefficient. Covariates entered: maternal education ($p = .24$), gestational age ($p = .06$).

* $p < .05$.

8.4 Chapter Summary

This chapter described the rearing environments of ME and non-ME children from birth up to age 9 years. It then examined the role of these factors in predicting prenatally ME children's increased risk for educational delay. Methadone-exposed children were more likely to be raised in environments characterised by frequent primary caregiver changes and, although not always in the care of their biological mother, these children were exposed to increased caregiver illicit substance use, more caregiver depression, and poorer quality caregiving environments. Primary caregiver changes and caregiver depression scores at 18 months were significant intervening factors. That is, ME children had poorer outcomes than comparison children on these caregiving factors which, in turn, predicted educational delay. Prenatal methadone exposure was not directly associated with children's educational delay after considering these caregiving factors. Supplementary analyses showed that ME children had higher rates of pre-school age impairments compared to non-ME children, which also predicted educational delay at 9 years.

CHAPTER 9

Discussion

9.1 Study Overview

Worldwide rates of opioid dependence among pregnant women have continued to increase, and more so in recent years, with some describing it as an epidemic (Committee on Obstetric Practice, 2017; Patrick & Schiff, 2017). Extensive research has shown that infants born to mothers treated with methadone during pregnancy are at elevated risk for a number of adverse neonatal and clinical outcomes compared to non-ME infants. Risks include a lower gestational age, restricted foetal growth, and a high likelihood of neonatal abstinence syndrome (Bakstad et al., 2009; Bier et al., 2015; Brogly et al., 2017; Cleary et al., 2012; Gray et al., 2010; Wouldes & Woodward, 2010). The growing body of literature indicates that ME children are at risk for psychomotor, social-emotional, language, and general cognitive impairments during early childhood (Hans & Jeremy, 2001; Hunt et al., 2008; Konijnenberg & Melinder, 2015; Konijnenberg et al., 2016; Melinder et al., 2013; Sarfi et al., 2013) that are likely to, as this study has shown, impact their later educational achievement.

To date, only one empirical study had investigated ME children's educational outcomes (de Cubas & Field, 1993). Methodological weaknesses of this limited empirical research, in part due to it being an early study, include: 1) the retrospective research design, 2) small sample, and 3) insufficient consideration of the confounding (other prenatal exposures, neonatal outcomes, and social background) and intervening (family) factors that may explain children's increased risk for educational delay. The current study was necessary to provide a rigorous investigation describing ME children's educational outcomes during the important middle childhood years. It was crucial to better the understanding of their academic skill development and achievement to age 9 years. The developmental processes that may contribute to lower reading and mathematics achievement for ME children was also of

critical concern, given that their risk for experiencing poor outcomes could be attributable to a range of adverse prenatal and postnatal risk exposures (Davie-Gray et al., 2013; Hogan, 2007; Lean et al., 2013; Oei et al., 2009; Rasmussen et al., 2016; Suchman & Luthar, 2000, 2001).

Rigorous and systematic research determining the processes that may contribute to educational delay for ME children is crucial for supporting the children's academic skill acquisition and mastery when they enter school. This will assist in ensuring them a positive educational trajectory and reducing their risk for cascading academic and psychological problems. Further, children's educational delay in the early school years will have ongoing impacts that extend beyond the child. These include the growing strain and pressure on their families, increased demands for educational services and resources, and increased economic costs, adding to the need for implementing timely interventions for children and families who need them.

To date, this thesis is the first to examine the educational outcomes of ME children at age 9 years. The following sections will discuss the study findings according to each of the study aims, followed by their theoretical and applied implications. Methodological considerations are also discussed, followed by suggestions for future research.

9.2 Educational Outcomes

The overarching aim of the thesis was to describe the educational outcomes of ME children compared to a regionally representative comparison group of non-ME children. Educational outcomes included: a) standardised reading and mathematics test performance, b) teacher ratings of achievement across the NZ curriculum, and (c) rates of enrolment in school-based special education services. It was hypothesised that ME children would have

lower standardised reading and mathematics achievement scores, lower teacher-rated school achievement, and increased rates of special education enrolment than non-ME children.

9.2.1 Children's standardised achievement test performance. Large between-group differences in children's performance on the standardised reading and mathematics achievement tests were found. The ME children had lower mean reading scores than the non-ME children across the Letter-word Identification, Reading Fluency, and Passage Comprehension subtests. These findings indicated that the ME children had consistently greater difficulty than the non-ME children with sight word reading and decoding, reading speed and accuracy, and reading understanding (Schrank & Flanagan, 2003). The poorer acquisition of these subcomponent skills, which are necessary for overall reading achievement and reading competence at age 9 years, meant that the ME children had lower global reading achievement compared to the non-ME children. Indeed, this was shown by the ME children's mean Broad Reading score, which was almost 1 SD lower than the non-ME children's mean.

Similarly, findings showed that the ME children had lower mathematics performance than the non-ME children, with moderate to large differences between the groups across these subtests. The ME children had greater difficulty with the core mathematical operations of addition, subtraction, multiplication and division, were slower and less accurate in completing these operations, and had greater difficulty with solving verbally presented, practical mathematics problems (Schrank & Flanagan, 2003). The ME children therefore demonstrated lower overall mathematics achievement, and this was reflected in their lower mean Broad Math Score, which was almost 1 SD below the non-ME group's mean score.

The significant achievement gaps between the ME and non-ME children's reading and mathematics scores has important educational implications. Non-ME children were close to 12-months ahead in skill attainment than the ME children. As such, ME children are likely

to be relatively impacted in terms of their capabilities for applying their current academic knowledge and skills in an educational setting. Further, the current discrepancies in achievement between the two group's reading and mathematics scores are likely to result in the Matthew Effect (Stanovich, 1986). That is, the discrepancies will become increasingly larger as these children progress through school. Children acquire reading and mathematics skills in a cumulative way, and studies have shown that children with lower skill acquisition learn at a slower rate in these subjects over time, while their higher achieving peers continue to gain academic skills at a faster rate (Caro et al., 2009; Morgan et al., 2008; Oei et al., 2017; Tagg & Thomas, 2007). The ME children's reading and mathematics skill acquisition occurred at a much slower or delayed rate, affecting the rate at which further skills in these core academic domains can be acquired. On the basis of previous research, this will have negative implications for their future achievement.

In contrast to the current study findings, the only other study investigating ME children's reading and mathematics achievement found no between-group differences (de Cubas & Field, 1993). However, there were a number of methodological issues in de Cubas and Field's study that limited the generalisability of their findings. These included a small sample size ($N = 20$), and the use of a non-ME comparison group comprised of clinically at-risk children with neonatal adversities (e.g. preterm birth). Current study findings support those of Oei et al., 2017 and Ornoy et al., 2001, who found evidence for lower average reading and mathematics achievement among illicit OE compared with non-OE children during middle childhood. Further, Oei et al. reported that there was an academic achievement discrepancy between the two groups of children that widened between the ages of 9 and 15 years.

Effect sizes calculated for comparative purposes in this thesis show small to moderate differences in the achievement scores between the groups in previous studies (Oei et al.,

2017; Ornoy et al., 2001). In the current study however, there were predominantly large between-group differences. These differences may be explicated by: a) ME children's mean scores being affected by the severely low scores of a small proportion of children, and b) their mean achievement scores potentially reflecting their mean IQ score, which was significantly lower than the non-ME group's mean IQ score (93.3 vs. 106.5). A finer grain analysis of the ME children's rates of reading and mathematics delay was conducted to explore these two possibilities, and the findings are discussed in section 9.2.2 below. Also discussed is the possibility that the differing magnitude of effects between exposed and non-exposed children's achievement scores in the current and previous investigations were due to methodological differences.

9.2.2 Children's educational delay. Based on their standardised test performance, a significantly larger proportion of ME than non-ME children had an educational delay. The largest between-group difference was for mathematics, with nearly half of the ME children demonstrating a delay (48% vs. 7%). The lower mathematics achievement of the ME group was therefore not skewed by a small proportion of children with severely low performance. The group difference in mathematics delay persisted following the exclusion of children with severe intellectual impairment from the analysis, indicating that a higher proportion of ME than non-ME children had a mathematics specific learning disability (40% vs. 7%). Mathematics delay was therefore not confined to children with severely low IQ scores. That is, regardless of IQ, a greater number of ME children demonstrated a clinically significant mathematics problem.

Methadone-exposed children were also at increased risk for a reading delay, with 40%, compared with 10% of the non-ME children, evidencing a delay in this academic domain. With more than one third of the ME group demonstrating a clinically significant reading delay, these results clearly show that the lower average reading achievement of the

ME group was not due to a small number of very low achieving children. Methadone-exposed children's higher rates of reading delay persisted even in the absence of severe intellectual impairment, with 30% of the ME group compared with 10% of the non-ME group demonstrating a reading specific learning disability. Similar to the mathematics results, this showed that even after excluding children with severely low IQ scores, a greater number of ME children had a clinically significant reading problem.

Additionally, more than half of the ME children (57% vs. 13%) were shown to have at least one domain of delay. The ME children's risk for having any educational delay was 4.5 times greater than the non-ME children's risk for having any educational delay. Similarly, nearly half (49% vs. 13%) of the ME group had a specific learning disability. This translated to a relative risk that was 4 times greater than non-ME children's risk for a specific learning disability. Clearly the ME group had greater difficulty in both acquiring and mastering the academic skills necessary for chronological age achievement in reading and mathematics. The majority of these children demonstrated performance equivalent to children more than 12 months below their chronological age in one, or both, of these subjects.

Corroborating the current findings, a previous study by Oei et al. (2017) showed that prenatally OE children had an increased risk of having any educational delay. Specifically, OE children's relative risk for having any educational delay from age 9 to 15 years ranged between 2.3 and 2.6 times greater than non-OE children's risk. Interestingly, the current ME group's relative risk for educational delay was almost two-fold higher than was reported for those OE children. Differences in methodology could explain this discrepancy, including differences in the measurement and defining criteria used to classify children's delay.

In their Australian study, Oei et al. (2017) analysed school-based educational achievement data derived from a National database, in which children's literacy and numeracy test results were graded into 10 standardised achievement bands. The achievement

bands were then used to identify children who did not meet the National Minimum Standard for their school grade, and this criterion was used to classify children as having an educational delay. Interestingly, 9-year-old children only needed to score within band 1 to meet the National Minimum Standard, but the general population of Australian children scored within band 4 on the reading and mathematics tests on average (Oei et al., 2017). Therefore, children with achievement scores in bands 2 and 3, although below average, were considered not to have an educational delay. In contrast, the current study used a single educational delay cut-point that reflected an approximate achievement delay of more than 12-months in chronological age on a standardised measure. This is described by the NZ Ministry of Education (2016d) as when children are eligible to receive school-based learning support. The current study's more stringent criterion was likely to have resulted in the classification of a greater proportion of children with an educational delay.

One potential issue with the educational delay criteria in the current study was use of the non-ME group's mean achievement scores to determine the educational delay cut-points, rather than using internationally standardised test norms. Of interest, the mean Broad Reading and Broad Math scores of the comparison group were 103.5 and 102.7, respectively (slightly higher than the standardised norm of 100). Using the comparison group mean - 1 SD to classify children as having an educational delay potentially decreases the specificity of the outcome measure. This may assist somewhat in explaining the current ME group's relatively high rates of educational delay. With this in mind, further efforts to identify whether or not the regional comparison group-based clinical cut-points were potentially over-identifying children as having a delay were made by assessing the proportion of children with severe, as opposed to mild reading and mathematics delays. Children with at least a 24-month chronological age delay (a severe educational delay) were identified using a cut-off score > 2 SDs below the non-ME group mean on Broad Reading and Broad Math.

9.2.2.1 Children's delay severity. There were higher rates of severe educational delay among the ME, compared with the non-ME, children. Nearly a quarter (21%) of ME children had a severe reading delay, and 18% had a severe mathematics delay. Methadone-exposed children had 5.3 and 4.5 times greater risks for severe reading and severe mathematics delays, respectively, and thus are clearly at elevated risk of educational delay even when a less stringent cut-off was employed to determine educational delay.

Of note is that Oei and colleagues (2017) matched their OE and non-OE groups for SES. In contrast, the current study comparison group was regionally representative and comprised larger proportions of both medium and high SES families than the ME group. Empirical research shows that children from low SES family backgrounds are at increased risk for educational difficulties compared with their high SES counterparts (Aikens & Barbarin, 2008; Caro et al., 2009; Fergusson, Horwood, & Boden, 2008; Finn & Rock, 1997; Gershoff et al., 2007; Howe et al., 2012; Kiernan & Mensah, 2009; Morrissey et al., 2014; Potter & Roksa, 2013; Sirin, 2005). By the end of compulsory schooling in NZ, 15-year-old children from the lowest SES backgrounds are 2 years behind children from the highest SES backgrounds on reading and mathematics (Easton, 2013).

Normative developmental theory would suggest that the socio-economic disadvantage of the ME children would place them at selectively increased risk for educational delay. It could be argued that understanding ME children's educational achievement and skill development in comparison to non-ME children who represent a more diverse range of social backgrounds is critical to avoid underestimating their educational delay. This will then permit a better understanding of ME children's educational achievement in relation to their typically-developing, same-age peers, assisting with timely educational service planning and provision. The impact of the ME group's social disadvantage on their educational outcome

over and above other present risks was considered in this study, as will be discussed later in the chapter.

9.2.2.2 Children's delay specificity. As an additional part of the first aim of this thesis, an assessment of the specificity of children's educational delay was conducted. The proportion of children with a delay in both reading *and* mathematics was determined. Methadone-exposed children's comorbidity rates were high, with more than half (54%) showing co-existing delays. In contrast, only a third of the non-ME children had an educational delay in both reading and mathematics. Of note, only a small number of non-ME children had any educational delay ($n = 9$) and could be included in the comorbidity analysis.

Current findings are supported by the rates of children's co-occurring reading and mathematics difficulties reported in the educational literature, with 30% to 70% of children identified as having both reading and mathematics delays (Compton, Fuchs, Fuchs, Lambert, & Hamlett, 2012; Willcutt et al., 2013). The mechanisms that may explain, in part, ME children's educational comorbidity will be expanded upon in later sections of the discussion. Briefly, from a dual hazard perspective, it is possible that the effects of prenatal methadone exposure on the developing brain may globally impact children's learning by affecting neural development and neurotransmission (Monnelly et al., 2018; Sirnes et al., 2017; Walhovd et al., 2012; Yuan et al., 2014). The high rates of reading and mathematics comorbidity among the ME children are also possibly a result of their relatively disadvantaged social background and child-rearing experiences. The ME group are likely to have had fewer exposures to both literacy and numeracy concepts during their pre-school years, placing them at increased risk for the slower acquisition and mastery of reading and mathematics skills than the non-ME comparison group at school-age (US Department of Education National Center for Education Statistics, 2001). Further, there are shared difficulties in a number of neurocognitive processes required for both reading and mathematics, such as processing speed, working

memory, and language comprehension, that potentially contribute to ME children's higher rates of delay in both reading and mathematics (Willcutt et al., 2013). Further research is needed to examine in more detail how these specific processes relate to ME children's achievement at school age to assess this latter speculation.

The current study also determined children's delay specificity by examining the reading and mathematics skills of children with delay. This was a within-group analysis to examine, in finer detail, the areas of weakness of the ME children, and to better understand which specific academic skills could be targeted for intervention for this group. The subgroup of reading-delayed children performed poorly on all three Broad Reading subtests (means 71.36 – 74.56). Methadone-exposed children with a reading delay demonstrated poor mastery for each of the component parts that contribute to their overall reading competence at age 9 years.

Chall (1983) describes 9-year old children as typically transitioning from *learning to read* to *reading to learn*, and in order to transition to this reading stage, children must have previously acquired a complex hierarchy of reading skills. These skills include grapheme-phoneme relationship knowledge, phonemic awareness, decoding and word reading fluency, and an age-appropriate receptive vocabulary to understand their reading material (Church, 2015). Although grapheme-phoneme knowledge and phonemic awareness were not specifically assessed in this study, these early reading skills are important for children to have acquired in a timely fashion for them to be able to acquire word decoding skills. Moving up the reading skill hierarchy, there was evidence from the ME children's low mean Letter-word Identification score that this group did indeed have difficulty with decoding and sight word recognition; skills that are pre-requisite and critical for fluent reading. The children's mean Reading Fluency score indicated slower and less accurate reading compared with their same-age peers, which challenged their ability to comprehend their text. Finally, the children

demonstrated poorer reading comprehension, with their low mean Passage Comprehension score indicating that, as a group, they were limited in terms of overall meaning that they could derive from novel passages of text (Church, 2015; McGrew et al., 2007).

The ME children with a reading delay (40%) clearly evidenced generalised reading difficulty. Across all subtests, the children's reading achievement was 18 to more than 24 months below their chronological age peers'. Typically, 9-year-old children have acquired word decoding skills and reading fluency, and are developing the ability to draw on the information in their text to understand or make sense of novel information. In contrast, the ME children were still developing word decoding strategies, resulting in slower and less accurate reading, and ultimately a poorer understanding of what they have read. Given that the earlier acquisition and mastery of the subcomponent reading skills is essential for children's reading competence to age 9 years and beyond, there is concern that these children will continue to read poorly compared to their same-age peers in the years to come. Importantly, it is likely that the differences in reading achievement between these two groups will only increase over time.

Methadone-exposed children's mathematics skill deficits were more specific than their reading skill deficits. Compared with their Applied Problem Solving skills, ME children demonstrated the most difficulty with Calculation skills, followed by Math Fluency skills. The children's low mean scores across all three subtests indicated poor overall mathematics achievement relative to their peers. However, the group did demonstrate that the rudimentary calculation skills that form the foundation for learning more complex mathematics concepts were the most difficult to understand. Concernedly the children were, on average, unable to solve any problems on the Calculation subtest beyond those involving single-digit addition and subtraction operations, and their average level of calculation skills could be translated as equivalent to those of typically-developing 7-year-old children (McGrew et al., 2007). If

children have not mastered basic numerical concepts, including operations with small quantities, they will be unable to perform increasingly difficult calculations involving larger quantities (Church, 2015; Dehaene, 2011).

Children must have also developed or acquired functional levels of fluency to perform mathematical operations efficiently. Fluency allows children to solve simple mathematical problems, such as single-digit operations, with a level of automaticity in which very little effort is required. Children who have not developed a sound understanding of number concepts, or a functional level of arithmetic automaticity, will be constrained in their acquisition of more complex operations that require additional cognitive energy, such as multi-digit and multi-step operations (Church, 2015; Patterson, 2015). Fluency is therefore an important skill to have acquired for overall mathematics achievement. However, the ME children with a mathematics delay in the current study showed severely low performance on the Math Fluency subtest, solving around 7 basic addition/subtraction facts per minute. This indicated that they were half as fluent as their same-age peers.

The ME children with a mathematics delay also had Applied Problem Solving skills that were 12-months behind their same-age peers' skills. These children found it difficult to solve problems without accompanying illustrations that visually represented object sets, and they performed poorly on operations that involved multiplication, division, simple fractions, decimals, and measurement concepts.

It was interesting to note that the ME group's mean Applied Problem Solving score was 13 points greater than their mean Calculation score, and 7 points greater than their Reading Fluency score. This was, at first, suggestive of a relative mathematical strength of the group. Interestingly however, the highest mathematics subtest score of the non-ME comparison group was also in Applied Problem Solving, and the subgroup of math-delayed ME children had a mean score nearly 1.5 SDs below the non-ME children's mean on this test.

This finding further highlights the need to compare ME children's standardised academic achievement scores to those of regionally representative children in future research, to avoid the risk of underestimating their educational difficulties.

The difference between the children's mean Applied Problem Solving scores and their Calculation and Math Fluency scores is possibly attributed to the teaching methods for mathematics that have been employed in NZ primary schools since 2001. Traditional methods of teaching mathematics involved rote learning basic facts in order to build fluency for obtaining the correct answer to a mathematics problem as quickly as possible (Patterson, 2015). In contrast, NZ children are currently taught to solve mathematical problems using a variety of practical strategies, with the aim of developing a more conceptual mathematics understanding (Ministry of Education, 2009a). That is, rather than focussing on building children's fluency in early operational or number fact skills, NZ children are encouraged to utilise their own preferred strategies for solving mathematics problems. Children's problem solving strategies could involve different ways of partitioning and combining numbers in addition and subtraction operations, as opposed to retrieving a basic fact automatically from memory. It is possible that the lowered emphasis on teaching children fluent concept recognition and early operational skills is reflected in the lower scores by both study groups on Calculation and Math Fluency compared to Applied Problem Solving.

To summarise, close to half (48%) of the ME children were identified in this study as having a mathematics delay. The results showed that these delayed ME children were approximately at the stage of mastering the early skills required for subsequent mathematical achievement, such as fluency in basic concept recognition and number fact knowledge. It could be extrapolated from the findings that the ME children were relying on their basic number sense and counting strategies to perform more simple mathematics problems, but were unable to move beyond counting to using part-whole strategies or derived facts to solve

more complex problems (Young-Loveridge, 2001). In contrast, their non-ME peers are most likely to be beginning to master a much wider range of operations that will enhance their later mathematics learning. For delayed ME children, the challenge that mathematics poses for them is only likely to increase as they mature, when mathematical tasks become more difficult and children are expected to integrate numerous concepts and process multiple pieces of information simultaneously.

9.2.3 Children's teacher ratings of school achievement. To date, this is the only study to have reported teacher ratings of ME children's achievement across a range of school curriculum subjects. Teachers reported that a larger proportion of the ME than the non-ME comparison children (26% – 65% vs. 8% – 22%) were performing below average to more than 12 months behind their same-age peers on each of the NZ curriculum domains. These were reading, mathematics, written and spoken language, art, and technology, with the exception of physical education. The latter finding may reflect that achievement in physical education typically does not require the literacy and numeracy skills that achievement in the other academic domains demands, particularly at lower levels of the NZ curriculum (Ministry of Education, 2007). There were also high rates of school performance comorbidity among the ME group, with more than half of these children rated as below average or delayed in three or more curriculum domains in relation to other children the same age.

The teacher ratings of children's school performance supported the ecological validity of the standardised test results, providing further evidence that the ME group had poorer educational outcomes than the non-ME group. This trend in the findings thus far, which is indicative of clinically significant educational delay in a large proportion of the ME group, suggests that ME children are more likely to experience difficulty in terms of their academic performance and achievement in the classroom. Supporting the findings from the children's WJ-III test results, the numerous school-based difficulties that many ME children in this

study experienced are likely to negatively affect their learning trajectory, and undermine their educational achievement in subsequent years.

9.2.4 Children's enrolment in special education. Methadone-exposed children were 3.7 times more likely than non-ME children to have received any special education support at school. School-funded teacher aide assistance was the most common, and was received by a quarter of ME children, compared to 8% of non-ME children. In addition, a higher proportion of ME children received support from Resource Teachers of Learning and Behaviour (6.5%) and Ongoing Resourcing Scheme funding (6.5%) compared to the non-ME children and the NZ student population (RTLb, 1.4% and 2%; ORS 0% and 1%, respectively). Methadone-exposed children are clearly overrepresented among the children receiving these higher-tier NZ special education services. Further, more ME children with any school-based support were receiving, compared to the non-ME children, a wide range of support services. These included literacy, behaviour, perceptual-motor, occupational/physiotherapy, and speech language programmes, showing that they were clearly a more developmentally compromised group of children.

One interesting finding from the current study was that less than half (43%) of the large proportion of ME children with a WJ-III achievement delay had no special education support at school. This could be due to the fact that it is difficult for NZ schools to acquire funding for children's specialised education services unless they have a severe developmental disability (Ministry of Education, 2012, 2016d). Only 1% of NZ children are eligible for the most intensive government-funded special education support (the ORS), and 2% are eligible for the more temporary RTLb support. Data describing the number of NZ children with the relatively widely available, school-deployed teacher aide support is difficult to obtain, as each individual school is responsible for assigning teacher aide support to the children who need it.

Understanding ME children's risk for educational delay is important to assist educational professionals in planning and implementing early intervention services. As discussed, ME children's high rates of educational delay will put increasing demand on the education system's funding and resources to support their learning. The Ministry of Education (2009a, 2009b) stated that a 6 to 12-month delay at age 9 years will result in children failing to meet their classroom's academic standards. It will also result in negative outcomes in terms of in terms of mastering the increasingly difficult academic tasks they will face as they progress through the school years (Church, 2015; Duncan et al., 2007).

Further, ME children's delays across multiple school achievement areas are likely to have negative psychological impacts. Children who experience academic difficulties will more likely experience social-emotional and behavioural difficulties (Chen et al., 1997; Lin et al., 2013; Moilanen et al., 2010; Wu & Kuo, 2015), with the continued school performance difficulties they are facing resulting in a negative self-concept and low self-esteem at school. Children with academic and social-emotional difficulties are also likely to experience rejection by their classroom peers, resulting in social isolation and further psychological distress (Deater-Deckard, 2001). The psychological sequelae of ME children with serious academic difficulties is of critical concern, with these children more likely to develop, or exacerbate, externalising and internalising problems, contributing to cumulative or cascading psychosocial problems in the long term.

9.2.5 Summary. The findings presented in the first results section of this thesis collectively supported the first hypothesis. The ME children had higher rates of reading and mathematics delay on a standardised achievement measure than the non-ME comparison children at age 9 years. Generalised difficulties across reading and mathematics domains were evident amongst the subgroup of educationally-delayed ME children, as were more specific difficulties in mathematical calculation compared to problem solving skills.

Methadone-exposed children also had relatively poor school performance across the NZ curriculum domains, and were more likely to be receiving special education at school. Due to the hierarchical and cumulative nature of reading and mathematics achievement it is unlikely that the group discrepancies found at this age will become less apparent as these children grow older. The presence of already large difficulties by age 9 years amongst ME children suggests an urgent need for information regarding their cause and development.

9.3 The Role of Confounding Factors in Explaining Between-Group Differences in Educational Outcome

The second aim of this thesis was to investigate whether prenatal methadone exposure increased children's risk for having a reading and/or a mathematics delay, or whether the ME children's increased educational risk reflected the numerous associated infant and maternal risks present at the time of birth. It was hypothesised that prenatal methadone exposure would remain associated with children's risk of having an educational delay, but the association would be explained in part by confounding factors. A wide range of potentially confounding factors was considered, including maternal social background factors, prenatal poly-drug use, infant gestation, birth parameters, and male sex.

Prenatal methadone exposure was shown to be associated with children's increased risk for educational delay over and above the influences of their mother's social background variables, their other prenatal drug exposures, and the infant's clinical characteristics at term. The link between methadone exposure and educational delay was not fully explained by other risk factors associated with maternal opioid dependence and MMT in pregnancy. However there were two confounders that explained, in part, ME children's increased risk of having an educational delay. These were maternal education level and infant gestational age, discussed below.

9.3.1 Maternal education. The level of education that children's mothers had attained at term was positively associated with their educational outcome. For both groups of children, lower maternal education level was uniquely associated with children's increased risk for educational delay when the effects of prenatal methadone exposure and other associated risks were adjusted for. This finding lends support to the associations found between lower maternal education and other prenatally substance-exposed children's increased risk of middle childhood educational delay in previous studies (Goldschmidt et al., 2004; Morrow et al., 2006; Oei et al., 2017). Taken together, the higher rates of educational delay among prenatally substance-exposed children compared to non-exposed children may be explained somewhat by the increased risk for substance-dependent pregnant women to also have low levels of educational attainment.

The association between maternal education level and educational delay in the current study remained robust when other maternal social background factors, including age, marital status, SES, and ethnicity were considered individually and as part of a cumulative social risk index. It has been theorised that an accumulation of contextual risks and their synergistic interplay, rather than any individual social risk factor alone, will most strongly predict children's increased risk for poor outcomes (Rutter, 2001; US Department of Education National Center for Education Statistics, 2001). Interestingly, when the maternal education variable was examined in relation to children's educational delay alone, the results were similar to when a cumulative social risk variable was assessed. These findings suggested that variation in maternal education may be more likely to differentiate ME children's family contexts, for example by impacting on the quality of the early learning environment and cognitive stimulation that parents provide (Konijnenberg et al., 2016). This, in turn, is likely to impact children's educational achievement. In support of this finding, general population studies have highlighted the importance of higher maternal educational attainment for

children's better cognitive outcomes such as educational achievement (Howe et al., 2012; Potter & Roksa, 2013), even when accounting for other maternal psychosocial risks (Lee, 2010; Perry & Fantuzzo, 2010).

9.3.2 Gestational age. Children who were born preterm were more likely to have an educational delay in the current study. For each additional week of gestation there was a decrease in children's odds of having an educational delay. Even though excluding children born very preterm at the study outset largely controlled for the effects of prematurity, the study included children who were late preterm born (34 to 36 weeks gestation). Gestational age is an important covariate to consider due to the well-known association between extent of prematurity and later neurodevelopmental impairment (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002; Talge et al., 2010), including in ME and OE samples (Hans & Jeremy, 2001; Oei et al., 2017; Salo et al., 2009).

Preterm birth (< 37 weeks gestation) has shown to be associated with an increased risk for educational delay amongst OE children and non-OE controls (Oei et al., 2017). Similarly, Salo et al. (2009) reported in their study of 3-year-old OE children that gestational age accounted for a significant amount of variance in general cognitive development scores. This indicated that a reduction in gestational length was associated with poorer cognition. What remains unknown however, and further complicates the interpretation of these converging findings, is whether lower gestational age results in poorer developmental outcomes, or these outcomes result from *in-utero* or neonatal complications associated with late preterm birth. Further research is needed to investigate this issue.

Interestingly in the current study, a gestational age by group interaction on children's continuous Broad Reading and Broad Math scores was found. This finding suggested that ME who are also born preterm represent a particularly vulnerable subgroup at risk for later educational delay. However, as already noted, a number of other factors that may be marked

by preterm birth could explain this association. Opioid-dependent mothers are more likely to experience obstetric complications than non-opioid-dependent mothers, including infection and placental abruption (Davie-Gray et al., 2013; Lam et al., 1992; Ludlow et al., 2004), which may contribute to early labour and associated adverse infant clinical outcomes. These pregnancy factors were not controlled for in this study. The finding is also interpreted with caution given the small number of study children ($n = 8$) that were born prior to 37 weeks gestation. Replication with a larger sample would be needed to validate these results which suggest, regardless of causal mechanisms, that gestational age is an important clinical factor associated with ME children's later educational outcomes.

9.3.3 Male sex. An unexpected finding was that male sex was not independently associated with educational delay in this study. Male sex has been consistently shown in the literature to be negatively associated with numerous neurodevelopmental difficulties including attention, behaviour, and educational achievement in the literature (Bada et al., 2011; Levine et al., 2012; Ministry of Education, 2016b; Nygaard et al., 2015; Oei et al., 2017; Sarfi et al., 2013; Slinning, 2004). Previous findings with the current study participants at 2 and 4.5 years showed that male sex significantly predicted children's lower cognitive, language and school readiness outcomes (Davie-Gray, 2011; Lee et al., *in preparation*). These findings suggested that boys would be particularly at risk for educational delay in this study.

The lack of a unique association between the male sex variable on children's educational outcome in the current study could be explained by the possibility of an increase in ME girls' risk for experiencing neurodevelopmental difficulties following the transition to school. Prenatally substance-exposed girls potentially demonstrate sleeper effects, that is, they may evidence cognitive difficulties relative to non-exposed girls during middle childhood, but not earlier. Nygaard et al. (2015) observed sleeper effects amongst a group of

OE girls who had a similar mean cognition score (e.g. IQ) to their non-exposed peers at ages 12 months, 24 months, 3 years, and 4.5 years, followed by significantly a lower mean score at 8.5 years of age. Whilst OE boys' neurodevelopmental problems, such as behavioural (Slinning, 2004) and cognitive difficulties (Nygaard et al., 2015), may be apparent from an early age, girls' early difficulties may be more subtle, and may increase over time with the influence of exposure to compounding environmental risks. Transitioning from the pre-school developmental stage could also negatively impact seemingly unaffected ME or OE girls' middle childhood outcomes, given the more challenging academic tasks and behavioural demands of a formal education setting compared with a pre-school or home setting. The findings highlight that careful assessments of both ME boys' and girls' learning progress in the early school years are necessary. These assessments will assist in the identification of children with academic difficulties who may not have shown evidence of neurodevelopmental impairment prior to school age.

9.3.4 Summary. Maternal education level and infant gestational age were significant confounders in the association between being born to a mother enrolled in MMT and having an educational delay at 9 years of age. Whilst maternal education and gestational age explained this association in part, significant between-group differences remained. These findings supported the second hypothesis, showing that ME children's increased 9-year educational risk was not fully explained by confounding factors. Importantly, it must also be recognised that the differing caregiving factors of the ME and non-ME children would have important intervening effects on their educational outcomes.

9.4 The Caregiving and Family Environments of Methadone-Exposed and Comparison Children

The final aim of this thesis was to assess whether ME and non-ME children differ on a range of caregiving factors from birth up to 9 years, and whether between-group differences in caregiving factors, in turn, predict differences in children's educational outcomes.

Methadone-exposed and non-ME children's caregiving environments and experiences were examined by assessing between-group differences across five variables that were considered important correlates of children's educational outcomes. It was hypothesised that ME children's caregiving to age 9 years would be characterised by increased adversity compared to non-ME children's. The descriptive findings from these analyses are discussed below, before describing the intervening role of specific caregiving factors in ME children's increased risk for educational delay in the next section.

9.4.1 Primary caregiver changes. Across the first 9 years there was a cumulative increase in the number of ME children who no longer lived with their biological mother. From birth to 18 months approximately 18% of children in the ME group experienced a primary caregiver change, and this increased to over half (59%) by age 9 years. A number of ME children had experienced considerable caregiver instability, indicated by the high rates of caregiver change for some of the children. It was found that some ME children had lived with up to seven different caregivers, whereas all of the non-ME children remained in their biological mother's care in their first 9 years.

Findings of the increasing rates of out-of-home care or caregiver changes are in keeping with other international studies investigating the outcomes of prenatally substance-exposed children. Hunt et al. (2008) reported that 28% of Australian ME children were no longer in their birth mother's care at age 18 months, increasing to 32% by 3 years of age. In addition, 44% of opioid and cocaine-exposed children in the US Maternal Lifestyle Study

were in out-of-home care at age 3 years (Messinger et al., 2004), and by age 11 years 65% had experienced at least one primary caregiver change (Levine et al., 2012). There is also evidence that the majority of Norwegian OE children were in non-maternal care since infancy (Nygaard et al., 2015; Slinning, 2004). Nygaard et al. (2015) reported that 93% of the Norwegian OE children they assessed at age 8.5 years were in out-of-home care, and 87% were permanently adopted before turning 12-months old.

The variability in out-of-home care rates reported across studies of substance-exposed children may be explained, in part, by the different international social policies for determining vulnerable children's removal from maternal care. In NZ, high-risk children are more likely to be placed in temporary out-of-home care than to be permanently adopted, and are therefore more likely to experience multiple caregiver changes (Lean et al., 2013). Additionally, the majority of ME children in non-maternal care in NZ are placed in kinship care, that is, with other family members. This is an interesting issue, as these high-risk children may continue to be raised in contexts that are similar to those characterising their family of origin, for example with increased rates of socio-economic adversity and single parenthood (see Table 6.5, page 80). Kinship home environments therefore have the potential to further compound the problem by precipitating the need for further caregiver changes for these high-risk children (Berger et al., 2009). Others have argued that kinship care may be more stable for children than non-kinship foster care (Iglehart, 1994).

Regardless of children's caregiver status, research has shown that children who cannot live in their biological mother's care are at risk of experiencing multiple caregiver changes, and this caregiver instability has been associated with children's increased risk of educational and mental health problems (Osborn & Bromfield, 2007). The often stressful and most likely disturbing childhood experiences that precede out-of-home care can result in negative outcomes for children, including poor academic achievement and psychological

well-being (Rosenthal & Hegar, 2016). This will be further discussed in the upcoming section.

9.4.2 Caregivers' illicit substance use. In the current study, close to a third of the ME children's caregivers reported using illicit substances at each of the 18-month, 4.5 and 9-year follow-up assessments. Further, nearly two thirds of the ME children had been in the care of an illicit substance user at any time (63% vs. 6%). Caregivers of the ME children predominantly reported using cannabis (55%), which was followed by sedative use (18%). Illicit stimulant (8%) and other opioid use (7%) were infrequently reported. In comparison, a study by Powis et al. (2000) found similar rates of cannabis (46%), but higher rates of sedative (68%) and stimulant (47%) use amongst treated and untreated opioid-dependent mothers. Further, Powis et al. found one third of methadone-maintained mothers with children over age 4 years continued illicit opioid use. The relatively lower rates of ongoing illicit stimulant and opioid use by caregivers in the current study may be due to a desirability bias effect resulting in caregiver's under-reporting use of these more dangerous illicit substances. A further explanation may be that, over time, less than half of the ME children were living with their biological mother in the current study. Interestingly, the current ME children were at increased risk of being raised by a caregiver who used illicit substances, regardless of whether or not that caregiver was their biological mother.

Illicit drug use by caregivers is problematic in that it can rapidly escalate and undermine household stability, resulting in caregivers who are emotionally and physically unavailable to their children due to intoxication, drug-seeking, or drug withdrawal (Barnard & McKeganey, 2004; Hogan, 2007). Ongoing substance use by caregivers can negatively impact their capacity for parenting their children, including reducing their responsivity and child involvement (Dawe, Harnett, Staiger, & Dadds, 2000; Hogan, 2007). These negative parenting behaviours, in turn, have negative impacts on children's educational achievement,

due to children's decreased exposure to a wide variety of language and cognitively stimulating experiences. Inadequate, neglectful, or abusive parenting due to caregiver substance misuse also places children at risk of entering into out-of-home care which, as noted, has a potential negative impact on their educational outcomes (Barnard & McKeganey, 2004).

9.4.3 Caregiver depression. Caregivers of ME children had more depression symptoms than comparison group caregivers at each follow-up assessment. Empirically, mothers' depressive symptomology would be expected to improve over time when they are in a treatment programme such as MMT (Schreiber, Peles, & Adelson, 2008), that involves therapy targeting substance abuse and psychological distress (Ministry of Health, 2014). Chronic depression, however, appears to be a common psychopathology problem in opioid-dependent women (Davie-Gray et al., 2013; Oei et al., 2009). Whether this association is due to drug effects or pre-existing psychiatric vulnerabilities is uncertain (Di Forti, Morrison, Butt, & Murray, 2007; Goldstein, Smith, Dawson, & Grant, 2015; Schreiber et al., 2008). However what is clear is that depression remained a significant problem for many of the ME children's caregivers.

The higher rates of depression among mothers of ME children have also been reported by Sarfi et al. (2013), who found 29% of mothers enrolled in OST had depression symptomology compared with 3% of non-opioid dependent mothers. No previous studies have reported ME school-age children's rates of caregiver depression. The current findings indicated that the ME children's high caregiver depressive symptomology was not driven by an increase in depression amongst children's biological mothers. Rather, ME children's caregivers had higher depression scores than the non-ME group from birth through to age 9 years, despite the increased rates of children residing in non-maternal care at each follow-up. It is possible that ME children are likely to be placed in the care of other family members

who may also be at risk for experiencing depressive symptomology, due to similar adverse psychosocial environments and genetic influences that predispose them to depression (Goodman & Gotlib, 1999; Nugent, Tyrka, Carpenter, & Price, 2011).

9.4.4 The quality of the early caregiving environment. Overall, the ME children's caregiving environments were characterised by fewer early learning opportunities, less cognitive stimulation, and less parental involvement and support than non-ME children's early caregiving environments (also see Davie-Gray, 2011). In the Maternal Lifestyle Study (Messinger et al., 2004), the OE group's mean HOME score at 10 months (35.57) was comparable to the current study ME children's mean score at 18 months (35.15), supporting the current findings. Interestingly however, Messinger et al. reported that their non-OE comparison group had a *lower* mean HOME score than their OE group (33.52, $p = .003$). This finding may reflect that the non-OE group in Messinger et al.'s study comprised children who were at risk for growing up in disadvantaged homes, including prenatally cocaine-exposed children and low SES controls.

From the available evidence, opioid-dependent caregivers raise their children in similar environments to non-substance-dependent, socially-disadvantaged, parents. The current study, however, compared the ME children to a more advantageous socio-economic group, and they were shown to experience fewer opportunities for promoting optimal child development and well-being at home. These early caregiving environment differences have important implications for ME children's early learning experiences, and subsequently their preparedness for acquiring and mastering academic skills at school age. Of note was that, in general, mothers with poor psychological well-being have been reported to raise their children in environments with similar characteristics to those of the current ME children (Goodman, 2007; Lovejoy et al., 2000; Suchman & Luthar, 2001). This is also likely to be an

important factor explaining the association between prenatal methadone exposure and a poorer quality home environment.

9.4.5 Caregiver school involvement. This is the first study to describe ME children's caregiver school involvement and engagement with their child's school environment. Teachers reported ME children's caregivers to be less likely to assist teachers both in and outside of the classroom, less likely to assist with other school activities, and less likely to attend parent-teacher meetings than comparison group caregivers. The relative psychosocial adversity of the ME children's caregiver's likely places strain on their ability to be physically involved with the school. These caregivers may be unable to visit the school due to inflexible work schedules, the inability to arrange or pay for childcare, or due to transportation difficulties (Jeynes, 2010; Lee & Bowen, 2006). Methadone-exposed children's families may also be unable to contribute to school events such as fundraisers that may involve donating money or other goods (Jeynes, 2010). Lower levels of maternal education amongst the ME children in the current study also likely contributed to their lower caregiver school involvement. Poorly educated mothers are more likely to have had their own negative educational experiences that, in turn, reduced their confidence and willingness to be involved with the school system (Epstein & Dauber, 1991; Lee & Bowen, 2006).

One consequence of low school involvement is that caregivers will fail to gain the important information from teachers and schools about how to support their child's learning at home. This, in turn, may negatively impact children's educational achievement. Research also indicates that a caregiver's physical involvement in their child's school may be a marker for more subtle aspects of their educational involvement, including the importance that caregivers place on education for their children, and the educationally-based parent-child communication and activities that take place in the home (Jeynes, 2010; Lee & Bowen, 2006). The finding that ME children's caregivers were less likely to be physically involved

with their education at school would suggest that these caregivers are also less engaged in promoting their education at home.

9.4.6 Summary. Longitudinal research findings from birth to age 9 years add to the small literature base describing the socio-familial environments of children who were prenatally exposed to methadone. The study findings provide support for the majority of existing findings. The ME children were raised in homes characterised by more environmental adversity, with higher rates of primary caregiver changes, more caregiver illicit substance use, and elevated caregiver depression compared to the non-ME group of children. Methadone-exposed children were provided fewer opportunities for daily cognitive stimulation by their caregivers, who were less responsive and involved in their toddler years. Methadone-exposed children's caregivers were also found to have less involvement in their child's schooling at 9 years.

9.5 The Intervening Role of Caregiving Factors in the Development of Prenatally Methadone-exposed Children's Educational Delay

It was hypothesised that the ME children's relatively adverse caregiving environments compared to their non-ME peers would, in turn, predict their poorer educational outcomes. It was expected that the observed differences between the ME and non-ME children's educational outcomes at age 9 years would be explained by intervening factors rather than the direct effects of prenatal methadone exposure *per se*. This hypothesis was supported, with prenatal methadone exposure predicting more frequent primary caregiver changes and elevated early caregiver depression scores which, in turn, significantly predicted children's educational delay. These influential intervening processes are examined in more detail below.

9.5.1 The role of children's primary caregiver changes. The frequency of primary caregiver changes was an important factor that explained ME children's increased

risk for having an educational delay. If a child was born to a mother enrolled in MMT during pregnancy they were more likely to have a greater number of caregiver changes up to age 9 years, which in turn was associated with increased risk of educational delay. Prenatally substance-exposed children who have experienced out-of-home care have been shown to have increased neurodevelopmental problems (e.g. Bada et al., 2008; Levine et al., 2012; Nygaard et al., 2015). However, the findings specifically regarding the educational outcomes of prenatally substance-exposed children who have experienced primary caregiver changes have been mixed. In support of the current findings, Levine et al. (2012) found that any caregiver change from age 1 month to age 11 years was associated with cocaine-exposed and non-exposed children's risk for special education enrolment. In contrast, Ornoy et al. (2001) found that OE children raised in out-of-home care had better educational outcomes than OE children in maternal care

Methadone-exposed children's educational outcomes will be influenced by the type of caregiving they receive both prior to and following a caregiving change. A change in caregiver is likely to take place following exposure to inadequate or neglectful caregiving, which is caregiving that is likely to provide little support for children's learning (Lean et al., 2013). Children's cognition has been shown to improve following placement in out-of-home care when they are placed in an optimal rearing environment with a supportive caregiver. Moe and Slinning (2001) assessed the cognitive development of 57 prenatally poly-drug-exposed infants at age 3 years, who had been adopted by specially trained caregivers before 1 year. Exposed children had lower cognitive development (MDI) scores than non-exposed children at ages 1, 2 and 3 years. However a developmental "catch-up" was evident when the MDI scores improved over the three years for the exposed children. A change in primary caregiver that results in exposure to a stable caregiving environment early on in life is suggested to have a similarly protective effect on substance-exposed children's academic

skill development, with early placement stability associated with more adequate caregiving and educational support than could be provided by the child's family of origin (Moe & Slinning, 2001; Ornoy et al., 2001).

In contrast, children who experience multiple primary caregiver changes and environments are more likely to have been exposed to consistently lower quality, maladaptive, or abusive caregiving (Bada et al., 2008; Suchman et al., 2006; Usher, Randolph, & Gogan, 1999). Children with an increasing number of primary caregiver changes will have limited opportunities to experience warm, nurturing, and invested parenting compared to children with a more stable caregiving environment, and this is likely to adversely impact their school readiness and academic skill development. Careful examinations of ME children's risk for entering into out-of-home care should be conducted in future, with the aim of identifying children who either require early out-of-home placement, or whose parents require family support to maintain a stable, and safe home in which to raise their children. Keeping families together when safe for children, or when necessary, establishing stable homes for them as soon as possible in order to optimise their early development and raise their educational achievement once they start school should be prioritised.

It must be noted that the current study's primary caregiver change measure has limitations that may have resulted in false negative rates. Children's caregivers were asked at each assessment wave to retrospectively report any primary caregiver changes since the previous follow-up. Any change in primary caregiver over each 6-month period of the child's life was recorded. The final measure was a sum of the total primary caregiver changes reported over the child's life from birth to age 9 years. This method potentially resulted in some error, for example if a child's new caregiver had little knowledge of their previous placements. As a consequence the overall number of children's caregiver changes may have

been underestimated. Future research could collate caregiver reports and official child protective service documents in order to accurately measure children's caregiver changes. Further investigation is also required to identify the caregiving environment factors that predicted ME children's primary caregiver changes and impacted their educational achievement. The specific parenting factors that contributed to children's primary caregiver changes, for example maltreatment and neglect, could not be delineated in this study.

9.5.2 The role of early exposure to caregiver depression. A second important influence in prenatally ME children's educational outcome at 9 years was caregiver depressive symptomology at age 18 months. Methadone-exposure status was consistently associated with caregiver depression from birth to age 9 years, however it was only the 18 month scores that had a significant intervening influence on children's educational outcome. This finding suggested that caregiver depression during infancy, as opposed to later in childhood, had pervasive effects on children's educational outcomes. Caregiver's elevated depression symptomology at any age has been associated with children's educational delay in both the substance-exposure (Levine et al., 2012; Marques et al., 2007) and general population literature (Shen et al., 2016). Further, it is frequently reported in the developmental literature that caregiver depression during infancy has important implications for children's later development (Hay et al., 2001; Kiernan & Mensah, 2009; Murray et al., 2010).

The most rapid period of brain development occurs over the first 3 years of a child's life, when existing brain structures and neural pathways that lay the foundation for subsequent learning and behaviour are sculpted through continuous interaction with complex and varying social and physical environments (Newman & Newman, 2017). Optimal cognitive development occurs in the context of daily numerous sensitive, contingent caregiver-infant interactions (American Academy of Pediatrics, 2000; Illig, 1998). Caregivers

who are responsive to their children's needs and communicative attempts, and those who afford their children cognitively stimulating interactions, materials and activities, assist with the shaping of their children's brain structures and the development of the neural connections that govern cognitive and learning functions in the early years. Infants who experience early exposure to positive parenting behaviours are more likely to have optimal cognitive outcomes throughout development, including educational achievement success (Gershoff et al., 2007; Kiernan & Mensah, 2009; Teo et al., 1996).

Depression negatively impacts the ability of caregivers to provide these optimal conditions for their infants, including for appropriately responding to the infant's needs and for involving themselves in their infant's learning activities. In a meta-analysis of 46 empirical parent-child interaction studies, Lovejoy et al. (2000) found that depressed mothers and mothers with higher self-reported depressive symptomology demonstrated more disengaged or uninvolved parenting behaviour including less playing, more ignoring, withdrawal or silence than non-depressed mothers. Depressed mothers also scored lower on positive parenting (pleasant, engaged and enthusiastic interactions) than non-depressed mothers. A child's age moderated the association between depression and positive parenting behaviour, with mothers of infants demonstrating less positive parenting behaviour than mothers of pre-schoolers. This is in support of the current study finding that the experience of maternal depression may be particularly salient for infants compared to older children.

Lovejoy et al. (2000) hypothesised that as infants begin to establish independence and autonomy, by beginning to make their own decisions and resisting parental assistance, there are added challenges for their caregivers that are in addition to the high demands of providing security, nurturance, and socialisation for their toddlers. Older children however are less dependent on their caregiver to initiate interactions, and are more capable of shaping parent-child interactions through learning how to engage and interact with their caregivers in their

play and other activities. The intensive parenting demands associated with challenging infant behaviour makes parenting an even more difficult task for depressed caregivers of infants and toddlers. With the high rates of depression among opioid-dependent women (e.g. Davie-Gray, 2011; Oei et al., 2009), it is unsurprising that research has shown mothers enrolled in MMT during pregnancy demonstrate less positive affect and less involvement with their children's development and learning than non-opioid-dependent mothers (Jeremy & Bernstein, 1984; Konijnenberg et al., 2016; Rasmussen et al., 2016; Suchman & Luthar, 2000).

Research examining the parenting styles and practices of ME children's caregivers and how they relate to their educational outcomes is still required. Investigations should continue to focus on assessing the quality of parent-child interactions amongst mothers enrolled in MMT and their young children. It is possible that, particularly with very young children who are most dependent on their parents and have the smallest behavioural repertoires, the disengagement and uninvolved parenting associated with depression could have enduring effects on their educational outcomes. As such, these findings would have important implications for the ongoing mental health services that many mothers enrolled in MMT require to improve their wellbeing and adequately support their children's development (Dawe et al., 2003).

9.5.3 Summary. There were significant intervening factors that explained the association between being born to a mother enrolled in MMT and having an educational delay at age 9 years, supporting the final hypothesis of this study. Prenatal methadone exposure predicted increased rates of primary caregiver change and higher early caregiver depression scores which, in turn, predicted educational delay.

Due to the very high rates of educational problems amongst the ME children in this study, it was deemed important to also examine whether the children at educational risk could

be identified prior to starting school. Therefore, an additional analysis was undertaken to determine the extent to which children's school readiness at age 4.5 years could predict their educational outcomes at age 9 years. These results are discussed below.

9.6 The Role of School Readiness in Predicting Educational Delay

9.6.1 Children's school readiness outcome. In line with a contemporary theory of school readiness, a "whole-child" approach was adopted to measure children's functioning across five interrelated neurodevelopmental domains at age 4.5 years (physical well-being and visual-motor development, social-emotional adjustment, approaches to learning, language, general cognition; High, 2008). Overall school readiness was indicated by the total number of domains in which a child demonstrated delay/impairment (Lee et al., *in preparation*). A significantly larger number of ME children (47% vs. 13%) had multiple domain impairments (≥ 2), indicating that ME children were beginning school with significantly more functional domain problems than their non-ME counterparts.

Similarly, ME and other OE pre-schoolers have been reported to evidence lower fine and gross psychomotor development (Hunt et al., 2008; Melinder et al., 2013; Ornoy et al., 1996), increased parent-rated internalising and externalising symptomology (Melinder et al., 2013; Ornoy et al., 2001; Slinning, 2004), lower inhibitory and attentional control and poorer working memory (Konijnenberg & Melinder, 2015), lower receptive and expressive language development (Hunt et al., 2008; Salo et al., 2009), and lower IQ scores than non-ME children (Hunt et al., 2008; Konijnenberg & Melinder, 2015; Konijnenberg et al., 2016; Nygaard et al., 2015; Ornoy et al., 1996). Of note is that the current group of ME children had rates of school readiness impairment similar to rates reported in other biologically vulnerable children. Two recent studies found that 47% and 44% of very preterm-born children in NZ and Australia, respectively, experienced multiple school readiness impairments (Pritchard et

al., 2014; Roberts et al., 2011). Findings collectively highlight that ME children are a group at high risk for a number of pre-school-age neurodevelopmental difficulties indicating poor school readiness, with these difficulties likely to impact on the children's transition to school and subsequent learning and achievement.

9.6.2 School Readiness Impairment and Educational Delay. Children's school readiness at age 4.5 predicted their later educational outcome at 9 years. School readiness was a significant intervening pathway, with prenatal methadone exposure associated with an increase in the number of school readiness domain difficulties children experienced at age 4.5 years which, in turn, was associated with 9-year educational delay. Other studies have found that prenatally substance-exposed children's physical health (Singer et al., 2008), internalising (Goldschmidt et al., 2004; Levine et al., 2012) and externalising behaviour (Levine et al., 2012), and general cognitive outcomes (Hurt et al., 2005; Levine et al., 2012) are negatively associated with their educational achievement. However, substance-exposed children's neurodevelopmental outcomes and educational achievement have predominantly been assessed concurrently (Goldschmidt et al., 2004; Hurt et al., 2005; Levine et al., 2012). Thus limited information is available about the impact that experiencing earlier difficulties, and importantly experiencing multiple difficulties, at pre-school age has on substance-exposed children's transition to school and subsequent achievement.

The importance of prior physical and visual-motor development, social-emotional adjustment, approaches to learning, language, and cognitive functioning for educational achievement has been well documented in the developmental literature, with difficulties in these individual domains at pre-school age evidenced to influence school adjustment and learning (Clark et al., 2010; Denton & West, 2002; Duncan et al., 2007; Maughan et al., 2003; Moilanen et al., 2010; Woodward et al., 2016). A previous NZ study also found that children with multiple school readiness domain impairments at age 4 years were at elevated

risk of later educational delay at ages 6 and 9 years (Pritchard et al., 2014). These findings corroborate the current study results, and imply that multiple domain impairments at school entry have negative cascading effects on children's educational achievement during middle childhood.

9.6.3 Summary. A measure of children's neurodevelopmental functioning at school entry showed predictive utility for determining their risk for later educational delay. Taken together, the findings that caregiving factors and school readiness were important influences in prenatally ME children's 9-year educational risk have theoretical and applied implications that will assist in our understanding of and response to prenatal methadone exposure.

9.7 Theoretical Implications

Findings from the current study make a unique contribution to the field, describing the educational outcomes of ME children in middle childhood (9 years). Findings from a closer examination of the factors associated with ME children's increased risk for having an educational delay lend support to the hypothesis that ME children represent a population at double jeopardy for poor developmental outcomes.

The current study findings provide support for Lester and Tronick's (1994) transactional systems model by demonstrating the influences of both the prenatal and postnatal environments in the development of ME children to school age. The model purports that maternal MMT in pregnancy will increase ME children's risk for early biological vulnerability. Children's development is further compromised by exposure to the psychosocial adversity that is associated with maternal opioid dependence. This study provided empirical support for Lester and Tronick's model by showing that frequent primary caregiver changes and early exposure to caregiver depression were important influences predicting ME children's educational delay at 9 years. The findings also extended their

model, showing that ME children's developmental outcomes are negatively influenced by their caregiving environment beyond the infancy period. Methadone-exposed children's increased rates of neurodevelopmental impairment at age 4-years also significantly predicted their educational delay at 9 years. In line with the model, these findings illustrate the transactional nature in which children and caregivers influence one another and child development. As such, the impacting role of both the family and child systems in shaping children's own developmental trajectory was highlighted in this study.

Further, findings from the current study support more general ecological theories of child development (i.e., Bronfenbrenner, 1979; Ryan & Adams, 1995) that suggest children's educational outcomes are impacted by their distal biological and social contextual factors through the mediating role of associated proximal factors. Ecological theories would imply that the interaction between a child's biological fragility and the response of their caregiving environment will determine their longer-term developmental outcome. In line with this, the results indicated that any potential long-term drug effect was indirect, mediated by environmental factors and other child attributes. The results indicated that ME children are more likely than their non-ME counterparts to grow up in homes characterised by low maternal educational attainment and experience sub-optimal parenting, as marked by their increased exposure to caregiver depression and an elevated risk for multiple primary caregiver changes. Whether or not the mutual parent-child relationship was implicated in the educational outcomes of ME children could not be determined by this study. However, systems theories implicitly suggest that early interactive processes between the ME child and their primary caregiver would play a role in establishing a foundation for optimal early neurodevelopmental outcome that contribute to their later outcome.

Finally, the current findings provide support for models that describe cumulative academic skill acquisition (Chall, 1983; Church, 2015). The exposure to the socio-

environmental risks observed for many of the ME children very likely led to their starting off at a disadvantage in their academic skill acquisition from school entry (Denton & West, 2002). Earlier studies have shown that multiple early neurodevelopmental domain impairments are more likely amongst children with multiple, early social risk exposures (US Department of Education National Center for Education Statistics, 2001). Children with early neurodevelopmental domain impairments, in turn, showed poorer reading and mathematics skill development after two years at school than non-impaired children (Denton & West, 2002; US Department of Education National Center for Education Statistics, 2001). The cumulative nature in which children acquire academic skills would explain how ME children's increased rates of neurodevelopmental difficulties at school entry have led them to fall further behind their more competent non-ME counterparts once they transitioned to school.

To an extent, this study provides support for the Matthew Effect, with at-risk pre-school children shown to fall behind their peers at school-age. This is important given that empirical research has shown that an even more pronounced widening of the gap between delayed and competent achievers occurs between middle childhood and adolescence (Caro et al., 2009; Oei et al., 2017). Thus, ME children are more likely than non-ME children to have a poor learning trajectory across the primary and secondary school years. Methadone-exposed children are at high risk to be over-represented in the 10% of early school leavers in NZ who fail to achieve formal literacy and numeracy qualifications (Ministry of Education, 2017b). The differences in school readiness between ME and non-ME children were associated with persistent educational delay. These early neurodevelopmental differences need to be addressed before these high-risk children start school, when the cumulative effects of multiple domain delays can seriously impact their long term school adjustment and educational achievement.

9.8 Applied Implications

The current study identifies multiple dynamic factors that contribute to ME children's educational outcomes. Several of these are familial and child factors that are potentially malleable and could be targeted for intervention, including parenting and parent-child relationship quality, maternal mental health, children's school readiness, and children's academic skill development. To be most effective, intervention efforts should be multi-disciplinary and prolonged, targeting a range of social, familial, and child variables as early as possible, with monitoring and support through school age.

Overall, there is strong evidence for positive family and child functioning outcomes following enrolment in programmes aimed at improving the parenting skills of women in MMT (Dawe & Harnett, 2007; Suchman et al., 2010; Suchman, Decoste, McMahon, Rounsaville, & Mayes, 2011). Around one third of the ME children in the current cohort experienced primary caregiver changes because of neglect or physical abuse (Lean et al., 2013). Multi-dimensional family intervention programmes have been shown to reduce child maltreatment. Dawe and Harnett (2007) reported that a multi-systemic home visiting intervention programme with a focus on parenting skills resulted in significant decreases in rigid, harsh parenting and child abuse potential for Australian women in MMT. Therefore a parenting programme to reduce the maladaptive parenting of many ME children in NZ may increase their caregiver stability and, in turn, improve their developmental outcomes.

Early Start is a parenting intervention programme available to families identified after birth as at-risk for compromised parenting (Fergusson, Boden, & Horwood, 2012) in Christchurch, NZ. The Early Start programme has been empirically shown to reduce child maltreatment amongst these families. Flexible programmes tailored to each Early Start family's needs were delivered by Family Support Workers. These included assistance with accessing child health care services, support for maternal social and emotional difficulties

stemming from inter-partner relationship problems, family violence, substance abuse, mental health problems and other sources of stress, advice and role modelling of positive parenting skills, and support to reduce family economic stress.

At 3 and 9-years post Early Start enrolment, intervention group children showed a greater number of positive outcomes than control group children (Fergusson et al., 2012). These outcomes included increased health check-ups, decreased hospital attendance for accidents and injuries, increased dental service enrolment, increased early childhood education and other community service enrolment, and decreased internalising and externalising behaviour problems. Early Start children continued to experience lower rates of punitive punishment and physical abuse, together with continued health and social-emotional improvements compared to controls to 9-years. Nonetheless, at both follow-up time-points the programme showed no effect on reducing a number of family outcomes, such as parental substance abuse and maternal depression (Fergusson et al., 2012).

Findings from the current study highlight the need for efficacious interventions for caregiver depression. Specifically, poor caregiver mental health during toddlerhood was related to later educational delay, suggesting that this may be a sensitive period for early holistic intervention and monitoring. There is emerging evidence that successfully reducing caregiver depressive symptomology is associated with both improvements in parent-child interactions and parental functioning, and child socio-emotional and cognitive outcomes (Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2015; Milgrom, Schembri, Ericksen, Ross, & Gemmill, 2011; Poobalan et al., 2007; Shaw, Connell, Dishion, Wilson, & Gardner, 2009). Treating caregiver mental health problems is important, as it may reduce ME children's risk of developing an educational delay.

Home-based interventions that support ME children from non-optimal early home learning environments are required. These interventions should aim to improve ME

children's school readiness, and thereby improve their acquisition of academic skills when they start school. Children's neurodevelopmental functioning prior to school entry is an important predictor of their later educational achievement. New Zealand research investigating home-based intervention programmes (e.g. Dosmukhambetova, 2017) has shown that supporting families of high-risk pre-school children before and during the developmental transition to school has positive impacts for children's classroom adjustment and academic achievement. Such interventions assist parents in creating supportive learning experiences in their day to day lives. Further, family interventions aimed at increasing parents' confidence and knowledge about fostering their child's learning has positive impacts on parental school involvement. This may encourage further learning opportunities in the home (BarHava-Monteith, Harré, & Field, 1999). Community and family support programmes that are implemented to improve ME children's school readiness and increase their parent's active role in their early learning may be effective in assisting a smooth transition to school, with increased home learning support and more positive academic trajectory to age 9 years as a result.

In addition, well-trained teachers and education professionals will be critical for the identification of those children most at risk following school entry, in order to implement special education programmes and prevent further learning delay. School-based programmes with an emphasis on the explicit teaching of fundamental literacy sub-skills such as *Quick60* (Chapman, 2016), and those with a focus on both number knowledge and basic facts as well as mathematical problem solving strategies (Neill, Fisher, & Dingle, 2010) have been shown to be effective at improving the educational achievement of children at high risk of academic failure.

The current research has shown that antecedents of frequent caregiver changes, early caregiver mental illness, and children's pre-school age functioning may need to be targeted in

order to prevent ME children's risk for middle childhood educational delay. Although school-based interventions may be necessary for the ongoing support of these high-risk children's education, early family-based intervention is most likely to ameliorate some of the early problems that initially contribute to these children's poor educational outcomes. A considerable challenge however is in enrolling and retaining hard-to-reach families, such as those affected by maternal opioid-dependence, in preventative treatment programmes, particularly those that are centre as opposed to home-based.

Methadone-maintained women are typically unlikely to enrol in psychosocial or parenting intervention programmes due to fears of child protective service involvement, and receiving stigma and judgment by service professionals (Donaldson, Spencer, Austin, & Moor, 2016). Yet these women may be more willing to seek medical and other service assistance during or shortly after pregnancy (Chan & Moriarty, 2010). Pregnancy may provide a "window of opportunity" for engaging methadone-maintained women and their infants in early home-based interventions targeting a range of maternal, family, and child factors using a holistic, multi-disciplinary approach (e.g. Dawe & Harnett, 2007; Dosmukhambetova, 2017; Fergusson et al., 2012). The complexity of early childhood, family, and wider socio-economic factors found to influence the educational achievement of ME children suggests that interventions that address functioning and interactions across multiple ecological domains will be necessary.

9.9 Methodological Considerations

The current study had numerous methodological strengths that addressed several limitations of previous research. These strengths included 1) the prospective longitudinal research design; 2) high recruitment of mothers enrolled in MMT during pregnancy; 3) recruitment of a regionally representative non-ME comparison group; 4) good participant

retention to 9 years; 5) use of psychological assessors who were blinded to children's group status; 6) multi-method measurement of children's educational outcomes; and 7) comprehensive measurement and inclusion of a number of potential confounding and intervening variables in the analyses. Nonetheless, there were limitations in the current study that are worthy of note. While some of the more specific limitations related to study findings have already been discussed, there are general limitations more common to the design and implementation of the research. These limitations were related to sample recruitment and retention, use of self-report measures, and additional covariate issues.

9.9.1 Sample recruitment and retention. Only the first 62 ME and 72 non-ME comparison children to consecutively turn 9 years old could be included in the current analyses due to thesis time constraints. To date, this is the largest sample of ME children to be prospectively assessed to middle childhood, making the sample size a considerable strength of the current study. Nonetheless, the study findings could differ slightly using the full data set. A larger sample will increase the statistical power to detect significant effects, potentially revealing associations between additional covariates and children's educational outcome. Given the good retention rates of this sample, there is confidence that the data will generalise to the population of ME children in the Canterbury region once the remainder of the cohort has been assessed. It must be noted that findings from the MIP study cohort children, who were recruited from one city hospital, may not generalise to other parts of the world, or indeed to other regions of NZ.

Another recruitment issue was identified when the non-ME children who were lost to follow-up were found to have lower maternal educational attainment than the non-ME children who were retained to age 9 ($p < .006$). This comparison group was therefore likely to be less representative of Canterbury families at age 9 years than they were at the term recruitment phase. Further, given the potential differential vulnerability between the two

study groups, the results should be considered keeping the even more advantageous social background of the non-ME comparison group in mind. Certain risk factors have been suggested, for example maternal depression, to influence children's development differently for children from socially advantageous compared to disadvantaged family backgrounds (Lovejoy et al., 2000). As such, the covariates included in the regression analyses would be likely to have a differential influence over ME and non-ME children's educational outcomes. In particular, there were some key study variables (e.g. primary caregiver changes, caregiver illicit drug use), that typically were not reported by comparison caregivers. Future research with a larger sample could examine the factors specifically related to ME children's educational achievement or delay using a within-group or mixed-level analyses. The current study aim was to include methadone group status as an independent variable and examine the role of prenatal methadone exposure in increasing children's risk for educational delay considering a range of other associated risks.

9.9.2 Self-report measures. The maternal psychosocial and caregiving data used in this study was measured predominantly through self-reports. This was the case for the primary caregiver change (as already described), and maternal/caregiver drug use variables. Additionally some of the 4.5-year child health and behaviour data was caregiver-reported. Importantly, there is the potential that these data are subject to bias, with social desirability influencing caregiver responses.

Maternal substance use during pregnancy was possibly under-reported in this study. The under-reporting of maternal substance use may be due to pregnant women not wanting to disclose their prenatal drug use, or possibly due to the effects of methadone or illicit substance intoxication making it difficult for women to report their drug use accurately. The identification of prenatal substance exposure is likely to be improved when biological screening methods are used in conjunction with a maternal interview. For example Lester et

al. (2001) found that 38% of pregnant cocaine/opioid using mothers denied substance use in an interview, that was later detected in infant meconium analysis.

In the current study, some self-reported maternal prenatal drug use was cross-checked by urine and meconium analysis. Urine samples were not routinely collected from all of the current study mothers during their pregnancies; rather it was collected at random.

Nonetheless, Davie-Gray et al. (2013) found that only a small proportion (10%) of the mothers from the current cohort had tested positive for drug metabolites in their urine than had initially disclosed drug use in an interview. Meconium was collected from the current study infants at term, yet this method for confirming or corroborating maternal reports of substance use may only be valid for detecting drugs used during the second part of the pregnancy (Lester et al., 2001). It is therefore possible that some prenatal substance exposure was not accurately recorded, particularly during the first trimester. This may have impacted the results regarding the potentially confounding nature of children's additional substance exposures during pregnancy.

Similarly, caregivers may have under-reported their illicit substance use at each of the study follow-ups. Caregivers may be particularly reluctant to report their illicit substance use if they had already experienced the removal of a child from their care under child protective services. Any maternal and caregiver under-reporting of prenatal and later substance use in this study was estimated as minimal however, given that there is no mandatory reporting of parental substance use in NZ. Further, mothers and other caregivers were assured that their interview data would remain confidential.

Desirability bias may also have affected some caregiver report data from the 4.5-year school readiness assessment. Two items that were included to assess children's health and physical development (incontinence and dental decay) were gathered by caregiver report. Similarly, children's social-emotional skills were assessed using the caregiver-completed

SDQ. It has been suggested that mothers may under-report problems for their children if they do not want them to be perceived negatively. In contrast, parents experiencing psychological distress themselves, which was more common amongst the ME group, may be more likely to report problems for their children (Fergusson, Lynskey, & Horwood, 1993; Najman et al., 2001).

9.9.3 Additional covariate issues. The third set of limitations in this study relate to additional confounding factors or potential unidentified third variable influences. Maternal enrolment in MMT during pregnancy could be considered a marker for a range of different obstetric and psychosocial risks that may influence children's long-term development. Although prenatal poly-drug exposures and a number of social background and infant clinical factors were considered in this study, under-control for confounding might have been an issue. A prenatal poly-drug score was used in this study, rather than assessing the potential influence of each individual substance on children's neurodevelopment. The method of summing children's different prenatal drug exposures was chosen to avoid problems with including highly associated covariates in the analyses. Further, researchers in this field have been increasingly recognising that, for many prenatally substance-exposed infants, the problem most commonly concerns one of poly-substance, rather than single-substance exposure (Lester et al., 2001; Nygaard et al., 2015). In addition, maternal poly-drug use during pregnancy has been suggested as indicative of increased foetal stress exposure, with each additional substance increasing the foetus's allostatic load and adversely affecting its developing stress response systems and later developmental outcomes (Conradt et al., 2014). Nevertheless, it is possible that collating different classes of drugs into one poly-drug exposure variable masked the effects of exposure to certain individual substances.

Another possible covariate of children's educational outcome that was not measured in this study is children's school and teaching quality. Although the two groups of children in

the current study predominantly attended public state schools, the opportunities provided by their schools, and the quality of the teaching that they received to support or advance their learning, is likely to have differed. There is evidence to suggest some school variables are predictive of children's educational success or failure. Teachers experienced in identifying children with lower school-entry skills and knowledge may be more proficient at fostering these children's early academic learning than less experienced teachers, with early effective teaching contributing to better student achievement outcomes (Lubienski, Lubienski, & Crane, 2008; Nixon, 2005; Stronge, Ward, & Grant, 2011; Zintl, 2005).

In addition, schools with greater financial resources may be more able to support the learning of disadvantaged children through increased access to additional teacher aides and other support services (Aikens & Barbarin, 2008; Lubienski et al., 2008; Rathbun, West, & Hausken, 2004). Bronfenbrenner and Morris (1998) suggest that the home and school are the two most influential contexts in which children's learning and development occurs during middle childhood. Methadone-exposed children's rate of learning once they have started school may therefore also be related to teaching quality and school resource availability, in addition to the socio-environmental and child predictors examined in the current study.

9.10 Future Research Directions

This study has broadened the current understanding of the associations between children who were prenatally exposed to methadone and their educational outcomes at 9 years of age. To date, no other existing studies have examined the middle childhood outcomes of ME children using a prospective longitudinal design, and included a range of confounders and intervening factors. The current study findings and their limitations have also highlighted several areas to be addressed by future research. These include examining additional prenatal mechanisms, caregiving processes, and children's associated cognitive

and behavioral developmental outcomes.

First, examining the possibility of a genetic transmission of risk for children's sub-optimal developmental outcomes was beyond the scope of the current study. There is now evidence of a genetic susceptibility for opioid dependence that may increase ME children's risk for greater NAS severity (Wachman et al., 2017). Further, there is likely to be a genetic association between an opioid-dependent mother's own cognition and behaviour, and her child's learning and behaviour outcomes (Ornoy et al., 2001). Lester and Padbury (2009) have also suggested that prenatal drug exposure triggers epigenetic alterations in the developing foetus, contributing to risk of longer-term negative outcomes. As such, certain genes or gene-environment interactions may moderate ME children's vulnerability to risk and subsequent developmental impairments. Genetic influences may therefore explain some of ME children's educational outcome heterogeneity. This is a hypothesis which could be explored in the future.

Additionally, an examination of the associations between specific parenting behaviours and children's later educational achievement would be useful to strengthen our understanding of how early caregiving experiences contribute to ME children's learning outcomes. Although present study findings suggest that differences in children's educational outcome were influenced by aspects of the caregiving environment, the specific parenting behaviours related to children's educational outcome require elucidation. An analysis of the observational parent-child interaction data collected at age 18 months would assist in explaining the critical parenting behaviours associated with ME children's early learning. Such data could inform on the specific parenting behaviours that potentially differentiated those ME children with and without educational delay, providing information on which skills to target for interventions with families affected by maternal opioid dependence.

Whilst several relevant intervening caregiving variables were measured, other potentially influential factors were not analysed. It is important to note that the self-report data describing children's family circumstances and home environments at each assessment wave was provided only by the child's primary caregiver. Influences exerted by other prominent caregivers and additional family members may have played an important role. These could have included paternal and extended family (e.g. Ornoy et al., 2001) and sibling influences (Dirks, Persram, Recchia, & Howe, 2015; Kiernan & Mensah, 2009). Future research could examine these additional influences on the target child's development, contributing to what we know about the childhood experiences of ME children, and their pathways to middle childhood educational success or failure.

A number of child competencies are also associated with educational achievement that should be investigated in future research. There are numerous cognitive skills in which children show immense development in the years following the school transition that could continue to impact their learning. Although it was beyond the scope of the current study to examine these concurrent skills, it is speculated that the co-occurring reading and mathematics problems in the ME group may be explained by underlying difficulties in attention, working memory, processing speed and verbal comprehension. These are skills in which ME children have demonstrated poorer development at pre-school age (Hunt et al., 2008; Konijnenberg & Melinder, 2015), and that are shared cognitive processes of reading and mathematics (Duncan et al., 2007; Willcutt et al., 2013). It is also widely recognised that executive and self-regulatory skills are essential for both a successful school transition and continued academic success (Blair, 2002; Clark et al., 2010; McClelland & Cameron, 2011; Woodward et al., 2016). Further research is necessary to examine how these skills may affect the academic learning of ME children following the transition to school. Determining which specific cognitive skills and deficits explain ME children's learning difficulties will assist in

tailoring school-based intervention or prevention efforts for this vulnerable population at school-age.

Children with educational difficulties are also more likely than academically competent children to have comorbid social-emotional problems. Externalising behaviour is particularly problematic amongst children with educational delay (Hinshaw, 1992b; Ministry of Education, 2016d). This study has shown associations between social-emotional problems at school entry and educational delay at age 9 years. Future research could then examine how educational delay at 9 years may either lead to the initial development of behavioural problems, or may exacerbate existing behavioural problems for children with prior social-emotional maladjustment (Masten et al., 2005; Moilanen et al., 2010). Examining whether there are cascade effects across developmental domains will further elucidate the educational trajectory for ME children.

One of the most important directions for future research will be to continue assessing the ME cohort to adolescence to monitor their educational progress and later psychosocial outcomes. During the critical middle childhood years, children transition from learning foundational reading and mathematics skills to being able to utilise those skills for advancing their own learning. It could be predicted that the educational trajectories of the ME and non-ME groups of children will further diverge in time, illustrating a clear Matthew Effect. The outcomes associated with educational delay for these children will also be important to monitor, including their mental health and behavioral outcomes. Elucidating the possible additive risk factors that contribute to later adverse adolescent outcomes or, conversely, protective factors that may serve to buffer ME children from those outcomes, may then better allow interventionists to discriminate between ME children whose difficulties are likely to be transient, and those that will require educational and psychosocial support. Children prenatally exposed to methadone who have severe educational delay will continue on a poor

overall developmental trajectory unless intensive and effective intervention takes place.

9.11 Conclusion

This study has contributed to the literature by furthering our understanding of the developmental outcomes of 9-year-old children who were born to opioid-dependent mothers in MMT during pregnancy. This is the first study to assess educational achievement in this high risk group of children, and to examine how prenatal methadone exposure and postnatal caregiving factors influence children's educational achievement at 9 years of age. As hypothesised, it was the environmental caregiving factors, rather than prenatal methadone exposure directly, that had the greatest effects and predicted the children's educational outcomes.

Findings from the current study provide support for, and extend Lester and Tronick's transactional systems model. Children prenatally exposed to methadone are a dual hazard group: they have greater prenatal adversity, and they are raised in environments characterised by greater psychosocial adversity than non-ME children. The model was extended by the finding that the ME children were at greater risk for developmental problems, with over half of these children shown to have significant educational delays. An increased exposure to an adverse caregiving environment, characterised by frequent caregiver changes and early caregiver depression symptomology, successfully predicted children's educational delay. Furthermore, these children were at an educational disadvantage before beginning school, as shown by their higher rates of school readiness impairment than non-ME children.

Educational achievement is critical for children's long term positive educational and psychosocial outcomes. There is a large literature elucidating successful interventions and prevention efforts to reduce and ameliorate poor educational outcomes among children. Key findings can be extrapolated to assist in guiding the early screening, identification, and

treatment of those children who are at greatest educational and developmental risk: specifically those raised in adverse environments. Reducing the risk of a perpetuating cycle of disadvantage in this high risk population through early family-based interventions is crucial for these children's optimal developmental outcomes.

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APPENDIX A



Health and Disability Ethics Committees
 1 the Terrace
 PO Box 5013
 Wellington 6011
 04 816 2403
 hdec@mh.govt.nz

28 November 2012

Dr Lianne Woodward
 Canterbury Child Development Research Group
 Psychology Department
 University of Canterbury
 Christchurch 8041

Dear Dr Woodward

Re:	Ethics ref:	URB/07/10/042
	Study title:	Neurodevelopmental Outcomes of Children Exposed to Methadone During Pregnancy at Ages 4.5 and 6 Years: Role of neuroanatomical and Socio-Environmental Factors.

I am pleased to advise that this amendment has been *approved* by the Southern Health and Disability Ethics Committee. This decision was made through the HDEC Expedited Review pathway.

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

Ms Raewyn Idoine
 Chairperson
 Southern Health and Disability Ethics Committee

Encl: appendix A: documents submitted
 appendix B: statement of compliance and list of members

APPENDIX B

Canterbury Child Development
Research Group
Department of Psychology
College of Science



CODE NUMBER

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9/ 10 YEAR FOLLOW-UP STUDY CONSENT FORM

- I have been invited to participate with my child in a study that is comparing the development of children who were and were not born to mothers on methadone maintenance during their pregnancy. I have read and understood the Information sheet dated November 2012.
- I have had enough time to consider whether we will take part in the study, and to discuss my decision with the researcher or a person of my choice.
- I know who to contact if I have any questions about the study.
- I understand that our participation in this research is **confidential** and that no material which could identify me will be used in any study reports, or made available to anyone else without my approval in writing.
- I understand my child will be videotaped during the procedure and that this information will only be used for further observation by the named investigators and the material will be secured and kept strictly confidential.
- I also understand that my child and I can withdraw from the study at any time.
- I understand the compensation provisions for the study.
- I am willing for the research team to contact my child's class teacher to obtain information on my child's school progress during the last year. YES/NO
- I agree to members of the research team having access to medical information about my child for cross checking the number and dates of any major or minor illnesses that I have recorded on the study forms. YES/NO
- I wish to receive a summary of the results of this study. YES/NO

I consent to take part in this study.

Parent/s Name: _____

Signature of Parent/s: _____ Date: _____

I consent to my child taking part in this study.

Child's name _____ Parent's Name: _____

Signature of Parent/s: _____ Date: _____

In my opinion, consent was given freely and the participant understands what is involved in this study.

Researcher's Name: _____

Signature of Researcher: _____ Date: _____

Canterbury Child Development
 Research Group
 Department of Psychology
 College of Science



CODE NUMBER

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Video Use Consent Statement (9/10) years

We are videotaping this session to help us record how your child responds to the activities, which we will do today. Most tapes are coded and scored by the Child Development Research Team and will never be seen by anyone else.

However occasionally, it is useful to be able to use short video clips for training or for presentations, with students and/or other professional workers. This may take place in Christchurch, elsewhere in New Zealand or abroad.

If you would be happy for us to use the tape of your child for this purpose, please indicate below. Your name and that of your child would always remain confidential and the videos would be presented in an anonymous way.

I give / do not give permission for the tape to be used for talks and presentations in Christchurch / elsewhere in New Zealand / abroad.

(Delete as appropriate)

Signed: _____

Name: _____
 (Please print clearly)

Date: _____

Canterbury Child Development
 Research Group
 Department of Psychology
 College of Science



**CANTERBURY CHILD DEVELOPMENT STUDY
 9/10-YEAR FOLLOW-UP**

We would like to thank you for taking part in the 9/10 year follow-up study. We are sending this form to show your child's teacher that you have given us permission to speak to them and access information from them in regards to your child's classroom behaviour. Your signature will be shown to them in case they have concerns regarding your consent.

Parental consent to take part in this study.

Parent/s Name: _____

Signature of Parent/s: _____ Date: _____

I consent to my child taking part in this study.

Child's name: _____

Parent/s Name: _____

Signature of Parent/s: _____ Date: _____

In my opinion, consent was given freely and the participant understands what is involved in this study.

Researcher's Name: _____

Signature of Researcher: _____ Date: _____

THIS STUDY HAS BEEN APPROVED BY THE UPPER SOUTH B REGIONAL ETHICS
 COMMITTEE

Reference: URB/07/10/042

APPENDIX C

SECTION A. ACADEMIC ABILITY

A: Essential Learning Areas

A.1 For how long have you been teaching this student?

Months

A.2 What year level is the student in at present?

Year level

Overall, how would you rate this child's progress in the following academic areas in comparison with other children of the same age?

	More than 1-year delayed	Below average	Average	Above average	More than 1- year ahead
Mathematics	1	2	3	4	5
English Language Spoken	1	2	3	4	5
English Language Written	1	2	3	4	5
Art	1	2	3	4	5
Physical Education	1	2	3	4	5
Health	1	2	3	4	5
Technology	1	2	3	4	5

A.8 How much support do you think this child gets from their parents in regard to their learning?

Not at all supportive

1

Somewhat supportive

2

Very supportive

3

Can't say

9

A.9 Have the child's parents been involved in any of the following ways?

Yes

No

a) Help in class

1

0

b) Help with out-of-class activities

1

0

c) Attend parent-teacher sessions

1

0

d) Other school activity

1

0

A.10 In your view, does this child currently have any learning problems?
If yes, please specify the nature of the problem.

Yes

1

No

0

A.11 In your view, would this child benefit from remedial tuition?

Yes

1

No

0

A.12 To your knowledge, has the child had any remedial help with school work in the last year?

If yes, please specify:

Yes

1

No

0

A.13 **Educational Support History**

a) Has this child ever been recognized as having special education needs?

Yes	1
No	0
Don't know	9

b) Please circle a number for each of the specific problem(s) below

	Yes now	In the past, not now	No
Learning difficulties	1	2	0
Specific learning difficulties (e.g. Dyslexia) *	1	2	0
Emotional and behavioural difficulties	1	2	0
Speech and language difficulties	1	2	0
Sensory impairment (Hearing)	1	2	0
Sensory impairment (Visual)	1	2	0
Physical disabilities *	1	2	0
Medical conditions *	1	2	0
Developmental delay *	1	2	0
Other *	1	2	0

*Please describe _____

c) Does this student receive ORRs funding?

No support, not being considered

0

Yes, does at present

1

Currently being considered

2

Not now, but has in the past

3

Has been refused

4

Not Applicable

9

d) Does this student have any of the following?

RTLB

Yes

No

1

0

IEP

1

0

Teacher Aide (please give details i.e. hours per week/subjects)

1

0

e) What is happening at the moment? (please circle all that apply)

Taught within school provision

Yes

No

1

0

Child is at special school

1

0

Child goes to special classes

1

0

Child has a special teacher

1

0

Hospital school

1

0

Educated at home

1

0

Child excluded from school

1

0

Something else (please tick and describe)

1

0

A.14: Is this child receiving any additional support services at school? (either individually or in a small group)

	Yes	No
Reading Recovery or similar special reading or literacy programme	1	0
Perceptual Motor programme	1	0
Teacher aide	1	0
Behaviour Management Programme	1	0
Occupational Therapy/Physio	1	0
Social Skills Programme	1	0
Speech and Language Therapy	1	0
Any other support. Please specify (i.e., language support, ESOL).....	1	0

A.15 Do you have any concerns about this child's achievement and behaviour?

APPENDIX D

Example of amended WJ-III Math Fluency Test format

1 - 1 =	0 + 3 =	2 + 2 =
4 - 2 =	2 + 1 =	3 - 3 =
0 + 0 =	3 - 0 =	2 - 1 =
2 + 4 =	5 + 0 =	3 - 1 =
1 + 6 =	4 + 4 =	5 - 0 =