EARLY-ONSET PSYCHIATRIC DISORDER IN PRESCHOOL CHILDREN BORN TO OPIOID-DEPENDENT MOTHERS

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ABSTRACT

Methadone Maintenance Treatment (MMT) is the most common treatment for women dependent on opioids during pregnancy. A growing body of research suggests that infants and children prenatally exposed to methadone and other opioids are at an increased risk of behavioural and emotional adjustment difficulties. However, the extent to which children prenatally exposed to opioids meet diagnostic criteria for mental health disorders is not known. The current study aimed to compare the early psychiatric outcomes and parent-reported behavioural and emotional adjustment difficulties of methadone-exposed (ME) and non-exposed comparison children at age 4.5 years old. The final aim was to examine the extent to which early-onset psychiatric disorders associated with prenatal opioid exposure might be explained by confounding infant, maternal and socio-familial factors.

The behavioural and emotional adjustment of 87 children born to mothers maintained on methadone during pregnancy and 103 non-exposed comparison children was evaluated in a structured parent interview when the children were 4.5 years old. Caregivers initially completed the Strengths and Difficulties Questionnaire (SDQ) as a screening measure for child behavioural and emotional problems and were then interviewed using the Development and Well-Being Assessment (DAWBA). The DAWBA online scoring system was subsequently used to generate provisional psychiatric disorder diagnoses, which were reviewed alongside other data by a registered clinical psychologist to assign final clinical diagnoses according to DSM-IV criteria. Measures of infant, maternal and socio-familial risk factors were also available from two earlier time points: late pregnancy/birth and at age 18 months.

Caregivers of ME children reported significantly higher levels of conduct problems ($p < .0001$), hyperactivity/inattention ($p < .0001$), emotional difficulties ($p = .01$), peer difficulties ($p = .002$), total difficulties ($p < .0001$), and significantly lower levels of prosocial behaviour ($p < .0001$) on the SDQ compared to caregivers of non-exposed comparison children at age 4.5

years. Caregivers of ME children also reported a significantly higher impact associated with the child's difficulties (p = .001). With the exception of emotional difficulties (p = .05), a significantly higher proportion of ME children had scores that fell within the clinical range for each of the other SDQ subscales. In terms of externalising disorder diagnoses, ME children had significantly higher rates of any diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD) (p = .001), Conduct Disorder (CD) (p = .003) and Oppositional Defiant Disorder (ODD) (p < .0001). Overall, ME children were not significantly more likely to meet diagnostic criteria for an internalising disorder. Furthermore, ME children were significantly more likely to be diagnosed with comorbid psychiatric disorders (p < .0001). After controlling for confounding variables, group status remained a significant predictor for any diagnosis of ODD/CD at age 4.5 years (p = .02). In contrast, other psychiatric disorder outcomes at age 4.5 years were largely explained by a range of confounding factors which included social risk, maternal psychopathology and poly-drug use.

The findings of the current study suggest that children born to mothers maintained on methadone are at an increased risk of early-onset psychiatric disorder, the most common of which were ADHD, ODD and CD. The risk for externalising disorder was much greater than internalising disorders at age 4.5 years. Findings tend to suggest that a complex interplay of teratogenic, biological and environmental influences may be contributing to ME children's mental health risk. This raises concerns about the future developmental trajectory of mental health difficulties in ME children and heightens the need for early intervention and ongoing social and clinical support. Future research is necessary to explore the relative contributions of postnatal risk factors that may potentially mediate the relationship between methadone exposure and externalising behaviour disorders in ME children at 4.5 years old.

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LIST OF ABBREVIATIONS

ADHD	Attention-Deficit Hyperactivity Disorder
CBCL	Child Behavior Checklist
CD	Conduct Disorder
CI	Confidence Interval
DAWBA	Development and Well-Being Assessment
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders- 4th Edition
ME	Methadone-Exposed
MM	Methadone-Maintained
MMT	Methadone Maintenance Treatment
NAS	Neonatal Abstinence Syndrome
ODD	Oppositional Defiant Disorder
OR	Odds Ratio
OUD	Opioid Use Disorder
SDQ	Strengths and Difficulties Questionnaire
SAD	Separation Anxiety Disorder
SES	Socioeconomic Status

1. INTRODUCTION

1.1 Methadone Maintenance Treatment

1.1.1 Opioid Use and Abuse

The use and abuse of opioids during pregnancy is a significant global public health issue. Maternal opioid use during pregnancy can pose a risk to the mother and her developing infant, which can, in turn, result in a cascade of adverse child neuroanatomical and developmental outcomes (Monnelly, Hamilton, Chappell, Mactier, & Boardman, 2018). Opioids are a class of drugs that are derived from the opium poppy plant *Papaver Somniferum* (Woodward, McPherson, & Volpe, 2018). The term "opioid" includes all substances that have morphine-like effects, including synthetic drugs such as methadone and natural opiates such as morphine (Ministry of Health, 2014). Previously, the most commonly used opioids were heroin and opium (Woodward et al., 2018). Now, synthetic opioids such as fentanyl, codeine and methadone are being increasingly used.

For centuries, opioids have been used clinically and recreationally as they provide pain management as well as additional euphoric effects (Woodward et al., 2018). Due to the euphoria experienced when taking opioids, they can be misused. Chronic and recurrent misuse of opioids can lead to addiction. Opioid addiction is often chronic, treatment can be difficult, and is often associated with mortality (Kolodny et al., 2015). The use and abuse of opioids increased significantly in the 20th century.

Heroin abuse in New York City escalated after World War II and deaths associated with intravenous heroin use surged from 7.2 per 10,000 deaths to 35.8 per 10,000 deaths between 1950 and 1961 (Joseph, Stancliff, & Langrod, 2000). The recent opioid epidemic, reported to be driven by the rapid increase in the use of prescription and non-prescription

opioids, is having a significant impact within first-world countries and has generated a public health crisis (Shipton, 2018). For example, within the USA, just under 400,000 people died as a result of opioid overdose between 1999 and 2017 (Scholl, Seth, Kariisa, Wilson, & Baldwin, 2018).

A similar trend appears to be occurring in New Zealand. Between 2001 and 2012, deaths in New Zealand related to opioids had an increase of 33%, with deaths likely attributed to prescribed morphine, codeine and methadone (Shipton, Shipton, Williman, & Shipton, 2017). Due to New Zealand's geographic isolation and various other factors such as a small marketplace and effective law enforcement (McMinn, 2014; Shipton et al., 2017), heroin is not as easily attainable as prescription opioids. Opioid dependence in New Zealand often involves the use and misuse of pharmaceutical opioids, the opium poppy and home-bake heroin (Ministry of Health, 2014). However, the misuse of both opioid analgesics and illicit heroin remains a significant issue and can lead to lasting impairment.

The use and abuse of opioids have direct effects on the brain and central nervous system. When an opioid travels through the bloodstream, it attaches to mu-opioid receptors (Kosten & George, 2002). Opioid receptors are located throughout different areas of the body, with the most pronounced effects on the central nervous system and gastrointestinal tract (Ministry of Health, 2014). When a person begins to take opioids, the mesolimbic reward system is activated and signals are created in the ventral tegmental area which then results in dopamine being released in the nucleus accumbens (Kosten & George, 2002). This process generates feelings of pleasure and other parts of the brain associate these feelings with the situations they occur in (Kosten & George, 2002). The person then develops conditioned associations and may experience cravings when encountering these situations/environments again (Kosten & George, 2002). When the person taking the opioid is not in significant pain and the opioid activates these reward processes (Kosten & George, 2002), the prolonged and

repetitive recreational use of opioids can occur. When a person becomes tolerant to increasing levels of opioids and becomes dependent on them, they are likely to develop withdrawals when no longer using the drug. Experiencing opioid withdrawal symptoms is a significant contributor to dependence and addiction (Kosten & George, 2002).

The chronic abuse of opioids can result in a diagnosis of Opioid Use Disorder (OUD). Opioid Use Disorder is characterised by a number of symptoms, including the inability to control opioid use, withdrawals, tolerance and intense cravings (American Psychiatric Association, 2013). Opioid Use Disorder symptoms reflect prolonged and compulsive use of opioid substances (American Psychiatric Association, 2013). Furthermore, opioid use during pregnancy can also pose a risk to the developing child and increase the need for social and medical services, which can impose economic burdens on society (Ross, Graham, Money, & Stanwood, 2015). Opioid Substitution Treatment, such as Methadone Maintenance Treatment (MMT), is the most widely used harm-reduction approach to treating individuals with OUD (Bawor et al., 2014).

1.1.2 Methadone Maintenance Treatment for Opioid Dependence

Methadone Maintenance Treatment was developed to help withdraw individuals from heroin. New Zealand was introduced to Opioid Substitution Treatment (OST) in the 1970s to manage opioid addiction and dependence (Deering, Sellman, & Adamson, 2014). Maintenance with methadone and buprenorphine, both opioids, are effective treatments used within OST in New Zealand. Methadone, a full mu-opioid agonist, is a synthetic opioid and is well known for its use as a treatment for opioid addiction. Buprenorphine is a semi-synthetic partial agonist that is also used to treat opioid addiction. Methadone has a long half-life of roughly 24 to 36 hours (Joseph et al., 2000), compared to heroin which has a relatively short half-life. The long half-life of methadone allows for administration once daily and can prevent withdrawal symptoms. Individuals enrolled in MMT are administered methadone

orally, either as a tablet or in liquid form (Bart, 2012). In addition to pharmaceutical treatment, MMT is often accompanied by psychosocial support. Methadone is only able to be legally administered in clinically observed and regulated environments, with restrictions on take-home doses (Wechsberg & Kasten, 2007).

Methadone Maintenance Treatment helps to reduce illicit heroin use, death from overdose and infectious disease transmission, and can improve the health of the individual (Ward, Hall, & Mattick, 1999). This process involves substituting an illicit substance such as heroin with a stable, pure dose of methadone (Burns, Mattick, Lim, & Wallace, 2007). Objectives of MMT in New Zealand include assisting individuals to safely withdraw from opioids, reduce crime, mortality, morbidity, and drug misuse, and importantly, to help improve the health and social and personal functioning of individuals enrolled in MMT (Ministry of Health, 2001). Despite the evidence that methadone is effective and safe for the individual enrolled in MMT, it is important to understand the potential impact of opioid exposure in-utero on the developing child.

1.1.3 Methadone Maintenance Treatment During Pregnancy

Methadone Maintenance Treatment is considered to be the primary treatment of choice for pregnant women with opioid dependency (Jones, O'Grady, Malfi, & Tuten, 2008). The volume of data about the safety and efficacy of MMT during pregnancy and breastfeeding is greater than for buprenorphine maintenance (Ministry of Health, 2014). Although, buprenorphine is now also increasingly being used in the U.S.A, due to the suggestion that it may be associated with lower rates of Neonatal Abstinence Syndrome (Jansson et al., 2019).

Pregnant women are a priority group for MMT in New Zealand (Ministry of Health, 2001). These pregnancies are deemed high risk (Ministry of Health, 2014). Pregnancy in opioid-dependent women who have not received treatment is associated with increased infant and maternal morbidity (Ministry of Health, 2014). Illicit use of opioids during pregnancy has

been identified as a risk factor for preterm labour and delivery, placental abruption, intrauterine foetal death and growth retardation, blood-borne viruses, and pre-eclampsia (Ministry of Health, 2014). The most common outcome of opioid use during pregnancy is Neonatal Abstinence Syndrome (NAS) which can occur in neonates after prenatal drug exposure (Larson et al., 2019). Neonatal Abstinence Syndrome also occurs after prenatal exposure to methadone. Other factors associated with maternal opioid use which can have an adverse impact on the developing child include the effect of multiple substances and psychosocial factors such as stress, maternal psychopathology and lifestyle, and poverty (Hans & Jeremy, 2001). This suggests the negative impact of maternal drug use on the developmental trajectory of a child is likely multifactorial. MMT can help stabilise and minimise the effects that opioid exposure can have on the developing foetus (Woodward et al., 2018). MMT can also prevent relapse, improve adherence with obstetrical care and help reduce foetal exposure to other risky maternal behaviours and illicit drugs (Jones et al., 2008).

Similar to opioids, methadone crosses the placenta and blood-brain barrier, exposing the developing foetus to exogenous opioids (Monnelly et al., 2018). In general, opioids act diffusely and can influence multiple neurotransmitter innervations and brain regions (Yanai et al., 2003). Pre-clinical studies have suggested that prenatal methadone exposure may alter myelination and the developing cholinergic, dopaminergic and serotonergic systems, resulting in a cascade of neuroanatomical changes (Monnelly et al., 2018). These early alterations in brain development may increase an infant's risk of early behavioural dysregulation and longer-term neurodevelopmental problems.

1.2 Outcomes of Methadone Exposure on Infant and Child Neurodevelopment

Although numerous short-term studies have been published on the developmental outcomes of infants who have been exposed to opioids in-utero, the research on behavioural

and emotional outcomes associated with prenatal methadone exposure in preschool and older children is scarce. Historically, existing research on the developmental outcomes of children exposed to opioids (including methadone) has focused on infant clinical, physical and cognitive outcomes. The following section provides a brief review of the findings on the effects of prenatal methadone exposure on infant neurodevelopment, with a more in-depth consideration of studies examining emotional and behavioural adjustment outcomes.

1.2.1 Neonatal Outcomes

Many studies have investigated infant clinical and physical outcomes such as head circumference, length, preterm birth and NAS, either at birth or shortly after delivery. Infants born to mothers maintained on methadone are at an elevated risk of being born preterm. When born close to term, methadone-exposed infants have been found to weigh less, have smaller head circumferences and are shorter in length than infants born to non-drug using mothers (Woodward et al., 2018).

Although methadone has been found to minimise the adverse effects that opioid exposure can have on the developing foetus, methadone-exposed infants are at risk of being born with adverse neonatal outcomes. Studies have reported elevated rates of preterm birth in opioid-exposed infants (Cleary et al., 2011; Hunt, Tzioumi, Collins, & Jeffery, 2008), which has been defined as the birth of an infant <37 weeks' gestation (Almario, Seligman, Dysart, Berghella, & Baxter, 2009; Cleary et al., 2011; Lim, Prasad, Samuels, Gardner, & Cordero, 2009). There is a substantial amount of research on the weight, head circumference and body length of ME infants and young children. Approximately 10% to 35% of ME infants are of low birth weight (i.e., <2500 grams) (Woodward et al., 2018). Various studies have reported decreased birth weight in ME infants (Hans, 1989; Hulse, Milne, English, & Holman, 1997; Hunt et al., 2008). Symmetrically smaller head circumferences have also been found in infants born to mothers maintained on methadone during pregnancy compared to comparison infants

(Kaltenbach & Finnegan, 1987; Rosen & Johnson, 1985). Multiple studies have investigated the average body length of methadone-exposed infants which have resulted in mixed findings. For example, Hans (1989) found that children aged two years who had been exposed to methadone in utero were shorter in height than the non-exposed comparison infants, however, the means for both groups were in the developmentally typical range. Studies have also reported significant differences in body length between methadone-exposed and non-exposed children that persisted throughout the preschool and childhood years (Hunt et al., 2008; Soepatmi, 1994) Although infants born to methadone-using mothers have been found to have disturbances in intrauterine growth, neonatal outcomes associated with untreated heroin use are considered to be more adverse than outcomes associated with methadone exposure (Woodward et al., 2018).

Neonatal Abstinence Syndrome (NAS) is prevalent in infants who have been prenatally exposed to methadone, due to the sudden end of drug exposure after the infant is born. Neonatal Abstinence Syndrome is a drug withdrawal syndrome that develops due to maternal opioid use during pregnancy and results in symptoms such as poor sleep, a high-pitched cry, irritability and uncoordinated sucking reflexes (Committee on Obstetric Practice, 2017). Numerous factors can influence how NAS is expressed in an infant, including poor maternal nutrition, obstetric and medical care, the timing of opioid pregnancy exposure and maternal stress linked to Opioid Use Disorder (Jansson & Patrick, 2019). Rates of NAS among infants born to mothers maintained on methadone during pregnancy ranges from approximately 13% to 90% (Woodward et al., 2018). As reported by Azuine et al. (2019), the prevalence of NAS in a longitudinal study of the Boston Birth Cohort had an increase that ranged from 12.1 per 1000 births in 2003 to 63.1 per 1000 births in 2012 (Azuine et al., 2019). The increase in NAS cases was consistent with the national trend increase. In summary, these findings suggest that

methadone-exposed infants are of increased vulnerability in-utero and during the neonatal period for various clinical outcomes.

1.2.2 Cognitive Development

A small number of studies have examined the short-term cognitive outcomes of infants who have been exposed to methadone in-utero, with longer-term follow-up studies being relatively scarce. Additionally, although a substantial amount of research has been published on general cognition, limited studies have assessed the risk of learning and executive functioning problems in methadone-exposed children (Woodward et al., 2018). Additionally, ME infants are reported to perform within normal ranges on general cognitive measures (de Cubas & Field, 1993). The most commonly reported measure of cognitive outcome in opioid-exposed children are the Bayley Scales of Infant Development (BSID) (Hans, 1989, Hunt et al., 2008; Rosen & Johnson, 1985; van Baar, Soepatmi, Gunning, & Akkerhuis, 1994), which assesses cognitive, motor, behavioural, and more recently language development in infants and young children. Findings on the cognitive outcomes of opioid-exposure tend to be mixed. For example, some studies have reported significant group differences between opioid-exposed and comparison children in measures of Intelligence Quotient (IQ) (Davis & Templer, 1988; Hunt et al., 2008; Sundelin-Wahlsten & Sarman, 2013), whereas some studies have reported no significant differences (de Cubas & Field, 1993).

Nelson et al. (2020) recently conducted a meta-analysis and systematic review of the cognitive development of young children who had been exposed to methadone or buprenorphine in-utero. Results revealed high heterogeneity between the studies, however, opioid exposure was significantly associated with lower cognitive test scores overall (Nelson et al., 2020). After statistically accounting for infant and maternal differences, notably prenatal tobacco smoke exposure, the significance of the association between opioid exposure and

cognitive test scores attenuated (Nelson et al., 2020). This suggests that a range of adverse socio-familial, maternal and infant factors may also contribute to lower cognitive test scores in opioid-exposed young children. However, further research is needed to investigate the long-term cognitive outcomes of ME children past the infancy stage.

1.3 Behavioural and Emotional Adjustment in Preschool Children

In the current study, the term behavioural and emotional adjustment difficulties encompass general behavioural and emotional problems as well as clinically significant adjustment difficulties, such as externalising and internalising mental health disorders. Both externalising and internalising problems are commonly presented in preschool children. These terms describe two broad dimensions of emotional, behavioural and social difficulties (Achenbach, Ivanova, Rescorla, Turner, & Althoff, 2016). Psychiatric disorders are also clustered according to prominent externalising and internalising symptoms (American Psychiatric Association, 2013). The major focus of this thesis is the psychiatric outcomes of preschool children that are discussed below.

Behavioural adjustment difficulties were the first key outcome of interest in the present study. Children with behavioural maladjustment may exhibit externalising behaviour difficulties that are often disruptive, aggressive and hyperactive (Hinshaw, 1987). Children can display oppositional behaviour, refuse to follow directions or requests from adults and are often stubborn (Wicks-Nelson & Israel, 2000). Issues with inattention, impulsivity and hyperactivity are also included within this construct. Within the current study, the term "behavioural adjustment difficulties" comprises these behaviours, as well as social functioning difficulties. Externalising behaviour problems can cause multiple disturbances for the child and their social environment and are often predictive of further behaviour problems and psychopathology (Reef, Diamantopoulou, van Meurs, Verhulst, & van der Ende, 2010). During early childhood,

externalising behaviours do not necessarily indicate or predict clinical problems (Wicks-Nelson & Israel, 2000). Problematic behaviours during the preschool years can be transient and age-appropriate. Many children display defiant and rule-breaking behaviour during early childhood (Hann, 2001), which can be developmentally normative behaviour. Externalising behaviours can reflect frustration and conflict relative to the child's young age (Campbell, 1995). Additionally, it can be difficult to determine the boundaries that separate abnormal and typical impulsivity, inattention and hyperactivity in preschool-age children.

Emotional maladjustment in preschool children was the additional key outcome of interest in the current study. Emotional adjustment difficulties are often characterised by internalising symptoms such as feelings of depression, anxiety and withdrawal. It is not uncommon for young children to have general fears and anxieties (Tandon, Cardeli, & Luby, 2009). During early childhood, anxiety is more prevalent than depression (Shapiro, 2019). When anxiety patterns are distressing, impairing, pervasive and uncontrollable, symptoms may reflect psychopathology (Tandon et al., 2009). Similarly, sadness, tearfulness and irritability in early childhood can indicate developmentally normative behaviours and emotions (Bufferd, Dougherty, & Olino, 2017). However, preschool children exhibiting behaviours such as decreased interest, pleasure and self-worth is less normative (Bufferd et al., 2017).

1.3.1 Externalising Disorders

Attention-Deficit Hyperactivity Disorder. Attention-Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder that often occurs during childhood and adolescence. It has been suggested that ADHD is a developmental impairment of executive functioning (Brown, 2002). Executive functioning underlies the ability to self-regulate, with self-regulation deficits being a central aspect of ADHD (Barkley, 2014). Across cultures, the prevalence of ADHD in children is expected to be approximately 5% (American Psychiatric

Association, 2013). According to DSM-IV diagnostic criteria, ADHD subtypes are distinguished based on two symptom dimensions; inattention and hyperactivity/impulsivity (Lahey et al., 1998). Symptoms of ADHD should be inconsistent with the child's level of development and must continue for at least six months (Buttross, 2007). Children with ADHD must also exhibit significant impairment in functioning, symptoms should cause impairment in more than one setting and have an age of onset before age seven (American Psychiatric Association, 2000).

The three subtypes of ADHD include predominantly Inattentive type, predominantly Hyperactive-Impulsive type and Combined type. Inattention is characterised by being easily distracted, decreased task persistence, difficulties with sustaining attention and disorganisation (Lahey et al., 1998). Hyperactivity/impulsivity is characterised by issues related to the regulation of motor activity and impulsive responses (Lahey et al., 1998). Hyperactivity and impulsivity are often more likely to be visibly identified due to the disturbance that can be caused by these behaviours (Buttross, 2007). Finally, ADHD Combined type incorporates maladaptive levels of both inattentiveness and hyperactivity/impulsivity (Lahey et al., 1998). Within this study, the term ADHD refers to all subtypes. Attention-Deficit Hyperactivity Disorder symptoms are often able to be distinguished from normative behaviours before the child turns four (American Psychiatric Association, 2013). In preschool-age children, the most common manifestation of ADHD is hyperactivity (American Psychiatric Association, 2013). This may be because children are not expected to pay attention for long periods in preschool, so inattentiveness may not be as observable during the preschool years compared to primary and secondary school environments. Children with ADHD can have difficulties with peer relationships and educational achievement and are at an elevated risk of developing Conduct Disorder and Antisocial Personality Disorder later in life compared to children without ADHD (American Psychiatric Association, 2013).

Oppositional Defiant Disorder. Oppositional Defiant Disorder (ODD) is defined as a recurrent and persistent pattern of hostile, defiant and negativistic behaviour, which leads to significant impairment in functioning and lasts at least six months (American Psychiatric Association, 2000). Children with ODD can exhibit anger and vindictiveness, with a majority of the behaviours being directed at the external environment, such as adults and authority figures (Steiner & Remsing, 2007). Keenan et al. (2011) examined oppositional defiant symptoms in a clinical sample of preschoolers and reported that the most common endorsed symptoms were defiance, loss of temper, deliberately annoying others and blaming others for their own mistakes. Although behavioural deviance is common in both ODD and ADHD, the argumentative and irritability that can be seen in ODD differs from the core symptoms that are observed in children with ADHD (Ghosh, Ray, & Basu, 2017). For an ODD diagnosis, symptoms must exceed developmentally normative behaviours according to the child's age, culture and gender (American Psychiatric Association, 2013).

Oppositional Defiant Disorder is less severe than other disruptive behaviour disorders such as Conduct Disorder and is often identified at an earlier stage of the child's development (Tolan & Leventhal, 2013). Specifically, ODD often emerges at the end of preschool/early school-age (Steiner & Remsing, 2007). The prevalence rates for ODD can vary depending on gender and age, but the average estimate is around 3.3% (American Psychiatric Association, 2013). Boylan, Vaillancourt, Boyle, and Szatmari (2007) systematically reviewed the prevalence rates of ODD in community samples of children and reported a range of 2.6% to 15.6%, with the preschool prevalence rate ranging from 9% to 12%. During childhood, ODD is slightly more common in males than females (American Psychiatric Association, 2013). It can precede the development of CD, severely delinquent behaviour, and substance abuse in children and adolescents (Steiner & Remsing, 2007). Additionally, symptoms of irritability and

anger seen in ODD can predispose children to the risk of developing an emotional disorder (American Psychiatric Association, 2013).

Conduct Disorder. Conduct Disorder (CD) is characterised by a persistent pattern of the violation of the rights of others or violation of major rules or norms (American Psychiatric Association, 2000; Keenan & Wakschlag, 2002). There are four major symptom categories of CD, which include aggression towards people and animals, property destruction, deceitfulness or theft, and serious rule violation (American Psychiatric Association, 2000). The individual must also be under 18 years of age for a diagnosis of CD (American Psychiatric Association, 2000; Frick, 2016). These symptoms must also cause notable impairment in the individual's functioning. Prevalence rates for CD range between 2% to >10% across cultures (American Psychiatric Association, 2013). Conduct Disorder can have an adolescent-onset or a childhood-onset before age ten, with significant differences between these two developmental trajectories (Frick, 2016). Childhood-onset CD is often characterised by the early emergence of mild conduct problems during preschool or elementary which then tend to persist and increase in severity (Frick & Nigg, 2012). Children with childhood-onset CD often display aggression, are more likely to be male and have poor peer relationships (American Psychiatric Association, 2013). Typically, CD is first identified in middle childhood or during adolescence (Tolan & Leventhal, 2013). However, conduct problems which originate during the preschool years often extend over the life course and can have significant consequences for further development (Fergusson, Boden, & Hayne, 2011). Conduct problems in childhood and adolescence can lead to adverse outcomes such as crime, suicidal behaviour, mental illness, antisocial behaviour, teenage pregnancy and substance abuse (Fergusson et al., 2011).

1.3.2 Internalising Disorders

In contrast to externalising disorders, internalising disorders are characterised by anxiety, depressed mood, and related cognitive and physiological symptoms (American Psychiatric Association, 2013). The emergence of internalising disorders during the preschool years is a considerably under-researched area, compared to research surrounding externalising disorders during these years. Internalising disorders during childhood include depressive disorders such as Major Depressive Disorder and Disruptive Mood Dysregulation Disorder, as well as anxiety disorders such as Generalised Anxiety Disorder, Separation Anxiety Disorder, Specific Phobia, and Selective Mutism (American Psychiatric Association, 2013). There has been debate surrounding whether preschool-aged children can present with clinical depression, with some theorists positing that it is not developmentally possible. However, the understanding of depressive disorders in early childhood has progressed and the presence of these disorders in young children has been identified (Luby, 2010). Young children with depression can often present with somatic symptoms including stomach aches, issues with appetite, headaches and sleep difficulties (Shapiro, 2019). Instead of presenting as sad, young children can exhibit irritability (Shapiro, 2019). In comparison to externalising behaviour disorders, internalising disorders are less commonly presented in preschool-aged children.

1.3.3 Comorbidity

An important issue with respect to early-onset emotional and behavioural problems concerns not just the extent of individual problems, but also that of comorbidity, which is defined as the two or more psychiatric disorders occurring simultaneously. However, amongst the literature, little research has been done on the comorbidity of psychiatric disorders in the preschool years in comparison to childhood and adolescence. Comorbidity appears to be a central aspect of psychiatric disorders during the preschool years (Egger & Angold, 2006).

Specifically, ADHD is highly comorbid with ODD, CD, and depressive and anxiety disorders (Cormier, 2008). The co-occurrence of ADHD and ODD has been consistently established in both clinic and community settings (Gadow & Nolan, 2002; Lavigne, LeBailly, Hopkins, Gouze, & Binns, 2009). Oppositional Defiant Disorder co-occurs with approximately one-half of children who meet criteria for ADHD Combined and one-quarter of children who meet criteria for ADHD Inattentive type (American Psychiatric Association, 2013). Approximately one quarter of children or adolescents with ADHD Combined have co-occurring CD (American Psychiatric Association, 2013). Boylan et al. (2007) reported the early onset of comorbidity between ODD and internalising disorders during the preschool years, with 10-20% of children with ODD diagnosed with a comorbid internalising disorder (Boylan et al., 2007). Within both the externalising and internalising groups, the sharing of environmental and genetic risk factors can potentially explain some of the comorbidities seen in both community and clinical samples (American Psychiatric Association, 2013). The combination of risk factors may result in the manifestation of both internalising and externalising behaviours (Boylan et al., 2007).

1.4 Literature Review

The behavioural and emotional adjustment of preschool children who have been prenatally exposed to methadone is under-researched. Although, despite the scarcity of longitudinal research, emerging literature has revealed significant associations between opioid exposure in-utero and behavioural and emotional difficulties. A majority of the following studies have almost exclusively relied on widely used caregiver-report measures of behavioural and emotional difficulties such as the Child Behavior Checklist (CBCL) (de Cubas & Field, 1993; Konijnenberg, Lund, & Melinder, 2015; Konijnenberg & Melinder, 2015; Nygaard, Slinning, Moe, & Walhovd, 2016; Ornoy, Segal, Bar-Hamburger, & Greenbaum, 2001; Soepatmi, 1994; van Baar et al., 1994) or the SDQ (Sundelin-Wahlsten & Sarman, 2013).

Additionally, some studies used caregiver-report measures to assess inattentiveness, hyperactivity and impulsivity (Nygaard et al., 2016; Sandtorv, Fevang, Nilsen, Bøe, Gjestad, Haugland, & Elgen, 2018; Sundelin-Wahlsten & Sarman, 2013), such as the parent- and teacher-report ADHD Rating Scale (ADHD-RS) and the Swanson, Nolan, and Pelham Questionnaire, Revision IV (SNAP-IV).

An important study within the literature is a retrospective medical review by Azuine et al. (2019), which is the only study to date which has examined the association between prenatal opioid exposure and psychiatric diagnostic outcome. Rather than relying on parental reports of child adjustment difficulties, this study investigated the rates of psychiatric diagnoses in children by reviewing medical records. However, this study likely underestimates the true prevalence of psychiatric difficulties in opioid-exposed children. This is because the sample is confined to the children who came into contact with clinical services and received a formal diagnosis. In contrast, the current study is based on a community sample of women and their children. Although they can be expensive, community samples are ideal as they are more representative of the general population (Egger & Angold, 2006). The study by Azuine et al. (2019) is reviewed further below.

Studies were primarily accessed through the University of Canterbury library resources and conducted using a key word search on major psychiatry/psychology and medical search engines such as PubMed and PsycINFO. The references list of relevant, previously reviewed studies were also used as a supplementary guide. Due to the lack of research on the effects of methadone exposure specifically, this review will also include findings on children who have been exposed to other opioids such as heroin and buprenorphine. Eighteen studies were initially reviewed, which included observational measures of child behaviour. However, five studies were dropped from the final review due to the current focus on diagnostic and parent-report measures. A study by Davis and Templer (1988) was also dropped from the final review due

to the focus on teacher-reported internalising and externalising difficulties. This review includes both longitudinal and cross-sectional studies (n = 12) with an age range of approximately preschool to middle childhood.

1.4.1 Studies Based on Parent Report

The following studies included in this section, organised by year of publication, review the extent of parent/caregiver reported emotional and behavioural adjustment in children prenatally exposed to opioids.

Wilson, McCreary, Kean, and Baxter (1979) conducted a cross-sectional study on the development of preschool children aged approximately 3-6 years who had been exposed to heroin in-utero. This study contained four groups; a heroin-exposed group (n = 22), a non-exposed drug-environment comparison group selected through methadone maintenance programmes (n = 20), a non-exposed high medical risk comparison group selected from hospital records (n = 15) and a non-exposed matched socioeconomic comparison group selected from local school readiness programmes (n = 20). Drug use data were obtained from medical records and the use of multiple drugs was noted in the target group of women who predominantly used heroin during pregnancy. Race, sex, age, SES and time spent in a school readiness programme were adjusted for in the analysis. As rated by parents on the Child Behavior Rating Scales, the heroin-exposed group experienced difficulties in both self and social adjustment ($p < .01$). Specifically, items that resulted in significant differences between the heroin-exposed group and comparison groups included aggression, impulsiveness, peer difficulties and temper. Although this study is dated, the use of multiple comparison groups to distinguish between environmental and teratogenic effects gives a clearer indication of the relationship between opioid exposure and behavioural outcome and the influence of socio-familial and perinatal variables. Later studies also employed this method of investigating heroin exposure in-utero (Ornoy et al., 2001).

de Cubas and Field (1993) conducted a cross-sectional study on the developmental outcomes of children exposed to methadone in-utero. A methadone-exposed group of children (n = 20) were selected from mothers participating in MMT during pregnancy/after birth. A majority of children from this group were Caucasian (17/20), which limits the generalisability of the findings. A non-exposed control group (n = 20) were selected from children seen in a local developmental evaluation clinic and were matched on demographic variables such as SES, ethnicity, maternal education, family structure, age/school grade level, sex, perinatal complications and alcohol and nicotine use. There were no statistically significant differences between both groups on these variables. Both groups had a wide age range of 6-13 years (M= 8.5 years & M= 7.8 years, respectively). Behaviour problems were measured on the maternal-report CBCL. The two groups differed on virtually all CBCL scales. In particular, methadone-exposed children scored higher on measures of hyperactivity ($p \leq .001$) social withdrawal ($p < .05$), depression ($p \leq .001$), somatic complaints ($p \leq .01$), aggression ($p \leq .01$), delinquency ($p \leq .001$), and internalising ($p \leq .001$) and externalising ($p \leq .001$) problem scales. This suggests that methadone-exposed children at school-age present with various externalising and internalising difficulties that are significantly higher than non-exposed children at school-age.

Soepatmi (1994) assessed behaviour problems in children prenatally exposed to either 1) heroin or 2) heroin and methadone (n = 91) between 4-12 years old in a case-control longitudinal study. Opioid-exposed children were enrolled in the infants of drug-dependent mothers study (IDDM) and were referred for long-term follow-up. No control group was included in this study; results were referenced to large-scale Dutch studies. Only 67/157 (43%) children were able to be followed up for more than a year. Behaviour problems were assessed using the CBCL, which resulted in a significantly larger proportion of children exposed to opioids obtaining a total behaviour problem score >90, compared to the reference group. Specifically, this was true for boys aged 4-5 years ($p < .001$) and girls aged 6-11 years (p =

.01). This suggests the presence of age and gender-specific effects. Social competence was also assessed on the CBCL. Mirroring the previous findings, the number of children who obtained a total competence score ≤10 was significantly higher in opioid-exposed boys aged 4-5 years (p = .011) and opioid-exposed girls aged 6-11 years (p = .009) compared to comparison children. However, this study was limited by the lack of consideration of confounding variables and no control group. Additionally, this study did not report further numeral information about results.

van Baar, Soepatmi, Gunning, and Akkerhuis (1994) conducted a prospective longitudinal study on children from birth to 5.5 years old who had been prenatally exposed to heroin, methadone and cocaine. Thirty-five infants of drug-dependent women were initially enrolled in the study after birth, who were also a part of the IDDM study included in Soepatmi's (1994) research. Almost all women who were addicted to drugs had been using combinations of multiple substances during pregnancy (94%), determined by urine toxicology analyses and maternal interviews. One-third of women were participating in MMT during their third trimester. Reference children (n = 35) were not exposed to substances in-utero and were also enrolled shortly after birth. At 4.5 years, the exposed children were reported to have more behavioural problems, depressive symptoms, and difficulties with interactions with peers and adults, and increased aggressive behaviour on the caregiver-report CBCL. However, at 5.5 years of age, behaviour problems were not present. This study did not describe the behavioural difficulties in opioid-exposed children further.

Ornoy, Segal, Bar-Hamburger, and Greenbaum (2001) investigated externalising behaviour difficulties in children aged 5-12 years born to heroin-dependent mothers in a case-control, cross-sectional study. Children were divided into five groups to explore the effects of environment and prenatal teratogen exposure. The first group of children were born to drug-dependent mothers and were living at home with them (n = 31) and the second group were born

to drug-dependent mothers but were adopted (n = 34) and the third group were born to heroin-dependent fathers and were raised by their biological parents (n = 33). All parents who used heroin also used a variety of psychoactive drugs. The fourth group comprised non-drug-addicted parents but low SES (n = 32) who were referred to the social services institute, and the fifth group served as control participants recruited from mainstream schools (n = 30). Caregiver-report behaviour measures included the CBCL and Conners Questionnaire with Deutch's modification for attention deficit. Approximately one-half of children born to mothers dependent on heroin and raised at home met the clinical cut-off point for ADHD (>21), which was significantly higher than control children (p < .01) and the remaining groups (p < .05). Approximately one quarter of adopted children and children born to heroin-dependent fathers met the clinical cut-off (p < .01) and 21% of children with environmental deprivation (p < .01) met the clinical cut-off point compared to no control children. All groups had significantly higher scores on the CBCL compared to control children. Externalising behaviour scores were highest in children who had been born to heroin-dependent mothers who were raised at home, with these children scoring significantly higher on the CBCL externalising behaviour subscale in comparison to all groups except for children born to heroin-dependent fathers. Heroin-exposed children also had significantly higher internalising difficulties than control children (p < .01). These results suggest elevated levels of externalising behaviour problems in opioid-exposed children may be due to an interaction of heroin exposure and environmental conditions.

Hunt et al. (2008) investigated the social maturity of children at 18 months and 3 years who had been exposed to methadone in-utero in a case-control, longitudinal study. Data on the methadone-exposed children (n = 133) were gathered from mothers who were being prescribed methadone during pregnancy and were compliant with their treatment. During their course of MMT, mothers were subject to regular maternal urine toxicology screenings for other

substances as well as regular clinic visits. Exclusion criteria included the presence of NAS without enrolment in a methadone maintenance programme or taking other substances of abuse. The non-exposed comparison group of children (n = 103) were recruited from antenatal clinics. Mothers were matched on factors such as ethnic background, age, previous obstetric history and height. Assessments were not completed blindly, as the assessments were conducted at the children's home. Only 50% of children were retained at the time of the three-year assessment. Primary caregiver-reported social maturity was measured using the Vineland Social Maturity Scale. Results revealed a significant difference between the methadone-exposed and non-exposed comparison children in social maturity, with the exposed children scoring significantly lower at both 18 months and three years ($p < .05$). This suggests that methadone-exposed children may exhibit lower levels of social competence than non-exposed children.

Sundelin-Wahlsten and Sarman (2013) investigated behavioural and emotional adjustment in children aged 5-6 years' old who were prenatally exposed to buprenorphine (n = 25) in a cross-sectional study. Initially, the mothers of 45 buprenorphine-exposed children were approached to participate and 28 accepted participation, but the number dropped to 25 due to unfinished tests. Instead of a control group, exposed children's results were compared to results from other studies. Mothers were enrolled in an opioid maintenance treatment programme at the time of pregnancy, with a mean buprenorphine daily dose of 15.1mg. Overall, 78% of women smoked during pregnancy, which was not described further. Outcome measures included the parent and teacher-report BROWN ADD Scales and SDQ. However, nine teachers did not return the BROWN and SDQ tests. Maternal self-report of exposed children's ADHD symptoms resulted in significantly higher scores on the BROWN ADD Scales compared to children without ADHD, but lower compared to children with ADHD. Comparatively, teacher-report on the BROWN ADD Scales resulted in scores corresponding for norms for

ADHD. There were no significant parent-reported problems on the SDQ. However, teachers reported elevated hyperactivity/attention (6.7 ± 2.7) and problem scores (≤ 7.0 ± 2.5). Taken together, teachers were more likely to report externalising behaviour difficulties compared to parents. This could suggest potential parental under-reporting or context-specific effects, as children's hyperactivity and inattention may be more clearly observed in the classroom. This study did not control for potential confounders, therefore, the conclusions drawn must be taken with precaution. The rate of non-completed psychometric tests is also of concern, as the children who were unable to be assessed could have had markedly different environmental characteristics to those who had available data. Additionally, significant differences were found in activity, attention, and memory between the children who did not have returned teacher reports and the remaining 16 children.

Konijnenberg et al. (2015) investigated the behavioural outcomes of preschool children who had been exposed to methadone (n = 24) or buprenorphine (n = 11) in-utero in a prospective cohort study. There was no non-exposed comparison group of children. Mothers were recruited from opioid maintenance treatment centres throughout Norway and self-reported the concurrent use of a range of licit and illicit substances such as tobacco, alcohol, amphetamines and marijuana during pregnancy. The authors controlled for child age, birth weight, and maternal employment and education in their analyses. Behavioural outcomes were measured using the caregiver-report CBCL. The mean CBCL scores fell within the normal range for both groups of children. This study found support for the maternal risk model as well as the combined model, but not the teratogenic model. Although there were no elevated behaviour difficulties in opioid-exposed children, results suggest that the behavioural outcomes could be a result of the combination of maternal/environmental factors in addition to opioid exposure, rather than solely opioid exposure. Another study on the same cohort of children as the previous study investigated attention problems in opioid-exposed children and comparison

children (Konijnenberg & Melinder, 2015). This study included a methadone/buprenorphine exposed group (n = 31) and a comparison group (n = 25). Attention problems were measured using the 'Attention Problems' subscale of the CBCL. After adjusting for the same confounders in the previous study by Konijnenberg et al. (2015), there were no significant group effects for attention difficulties according to parent report. These results mirror the previous CBCL findings reported by Konijnenberg et al. (2015), suggesting that methadone and buprenorphine-exposed children are not at an increased risk of caregiver-reported behavioural issues.

Nygaard et al. (2016) conducted a prospective, longitudinal study on the attention and behaviour problems of children who had been prenatally exposed to opiates and multiple other substances. The drug-exposed group (n = 72), recruited from an in-patient clinic, and the non-exposed comparison group (n = 58), recruited from local health centres, were followed up at ages 4 ½ years old and 8 ½ years old. Twenty-six participants were lost at the 8 ½ year follow-up, with 79% of exposed children and 81% of non-exposed children retained. The use of multiple substances during pregnancy such as tobacco (n = 72), opiates (n = 39), alcohol (n = 9), and benzodiazepines (n = 8) were reported via maternal self-report or from medical staff report and records. This study adjusted for parental SES, birth weight, gestational age, and time of assessment. Inattention, hyperactivity and impulsivity were assessed using the parent and teacher-report ADHD Rating Scale. According to caregiver report, 25% (n = 14) children who were exposed to opiates and other substances during pregnancy had scores that indicated ADHD problems, and according to teacher report, 17% (n = 9) of the exposed children had scores that indicated ADHD problems. No comparison children obtained scores above the cut-off point for both parent and teacher report. Nygaard et al. (2016) also compared drug-exposed children to comparison children at 8 ½ on the CBCL and Teachers Report Form (TRF). There were significant group differences in caregiver-reported externalising (p = .05), attention (p = .005), and social problems (p = .02). Twelve children (21%) in the exposed group had scores

that were ≥ 95th percentile on the CBCL total problem scale, compared to one comparison child. Teachers also reported significantly higher levels of externalising and attention difficulties in the exposed group. Parents also reported an increase in externalising and internalising difficulties over time. Unlike many other studies, this study included the use of both parental and teacher reports which was useful for examining behaviour across different settings.

Rates of inattention, hyperactivity and impulsivity in children exposed prenatally to opiates and other illicit drugs were investigated by Sandtorv et al. (2018) in a cross-sectional study. The exposed group (n = 57) were a hospital-based group of children who had a medical history of prenatal drug exposure and had symptoms of developmental impairment. Of the 128 children referred, 57 children had the relevant measures completed. Information about drug exposure during pregnancy was gathered from medical records and maternal self-report. The comparison group (n = 171) included children who had not been prenatally exposed to drugs and were participants in a population-based, longitudinal study. The reference group were matched on age and sex. Both groups of children were aged approximately ten years old at the time of assessment. Inattention, hyperactivity and impulsivity were measured on the Swanson, Nolan, and Pelham Questionnaire, Revision IV (SNAP-IV). Caregivers reported a significantly higher number of symptoms of ADHD Combined (M= 19.65 vs M= 4.13; p < .001), inattention (M = 10.79 vs M = 2.72; p < .001) and hyperactivity/impulsivity (M = 8.86 vs M = 1.42; p < .001) compared to the reference group, suggesting opiate-exposed children are at risk of presenting with increased levels of symptoms for all ADHD subtypes. An important limitation in this study is the limited consideration of the effects of poly drug use, as authors could not determine the use of alcohol or tobacco during pregnancy.

Overall, the majority of the above studies suggest that opioid-exposed children are at an increased risk of both externalising and internalising difficulties. In particular, opioid-exposed children appear to be at an increased risk of presenting with parent-reported

inattentiveness, hyperactivity, impulsivity, and/or aggression (de Cubas & Field, 1993; Nygaard et al., 2016; Ornoy et al., 2001; Sandtorv et al., 2018; Soepatmi, 1994; Wilson et al., 1979). Studies also reported increased levels of internalising (de Cubas & Field, 1993; Ornoy et al., 2001) and social difficulties (de Cubas & Field, 1993; Hunt et al., 2008; Nygaard et al., 2016; Wilson et al., 1979) compared to comparison children. However, some studies did not report elevated behavioural and emotional adjustment difficulties in opioid-exposed children on parent-report measures (Konijnenberg et al., 2015; Konijnenberg & Melinder, 2015; Sundelin-Wahlsten & Sarman, 2013; van Baar et al., 1994). Table 1 presents a summary of the above studies and specific methodological limitations. Amongst the previous research, there is a lack of studies examining psychiatric outcome in opioid-exposed children. A recent study on the association between opioid exposure and child mental health outcome is reviewed below.

1.4.2 Mental Health Outcome Studies

To date, the longitudinal study by Azuine et al (2019) is the only study that has examined associations between prenatal opioid exposure and children's later risk of a psychiatric diagnosis. Based on the Boston Birth Cohort, this sample consisted of 8509 mother-newborn pairs enrolled at birth. A subset of these children had prenatal opioid exposure (n = 454), based on a clinical diagnosis of NAS or maternal self-report of opioid use during pregnancy. Mothers with opioid exposure also self-reported the use of a range of substances during pregnancy such as marijuana, cocaine, stimulants, and crack. A large sample of mother-child dyads (n = 3153) were enrolled in a postnatal follow-up and were followed from birth to 21 years old. Psychiatric outcome (ADHD and CD/Emotional Disturbance) was assessed by review of ICD-9-CM and ICD-10 codes from children's electronic medical records and was examined by child age groups (<6 years vs ≥6 years). Self-reported maternal educational level, marital status, household income, maternal age, and ethnicity were adjusted for, as well as low birth weight and preterm birth. For children who had medical records for their first six years

of life (n = 3106), children prenatally exposed to opioids had higher levels of Conduct Disorder/Emotional Disturbance diagnoses compared to non-exposed children, with a non-adjusted OR of 2.17 (95% CI, 1.35-3.49) and an adjusted OR of 2.13 (95% CI, 1.20-3.77). In contrast, for children with records after age six (n = 2391), children who were prenatally exposed to opioids had higher levels of diagnoses of ADHD compared to non-exposed children, with a non-adjusted OR of 2.86 (95% CI, 1.67-4.91) and an adjusted OR of 2.55 (95% CI, 1.42-4.57). This study mainly consisted of a minority, low-income sample, hindering the generalisability of the findings. Nonetheless, these findings are an important and informative addition to the previous research on the mental health diagnostic outcomes of opioid-exposed children.

Table 1

Studies on Parent-Reported and Diagnostic Measures of Behavioural, Emotional and Social Adjustment Outcomes of Children Prenatally Exposed to Opioids

Study	Research design	Developmental domain	Participants	Age(s) at assessment	Retention at last assessment	Poly-drug use during pregnancy	Examination of Confounding Variables	Key outcome measures	Key Findings	Limitations
Wilson et al., 1979	Cross sectional	Behavioural and social adjustment	1) Heroin-exposed group: *n* = 22 2) Non-exposed drug environment comparison group: *n* = 20 3) High-risk medical comparison group: *n* = 15 4) SES comparison group: *n* = 20	Mean: 4 years 7 months. Range: 3 years 1 month to 6 years 4 months	N/A	Seven women reported the abuse of multiple substances such as codeine, methadone, barbiturates, tranquilizers, and Robitussin	Adjusted for race, sex, SES, age, and amount of time spent in a school readiness programme	Caregiver-report Child Behavior Rating Scales	Significant between group differences in self-adjustment ($p < .05$), physical adjustment ($p < .05$) and social-adjustment ($p < .01$)	•Small sample size •No further numerical information about results •No consideration of poly-drug use in analysis •Could not verify drug use
de Cubas & Field, 1993	Cross sectional	Behavioural and emotional adjustment	1) Methadone-exposed group: *n* = 20 2) Non-exposed comparison group: *n* = 20	1) Mean: 8.5 years (range: 6-13) 2) Mean: 7.8 years (range: 6-13)	N/A	All mothers self-reported moderate use of cigarettes and alcohol	Matched on perinatal complications, age, sex, ethnicity, familial structure, SES, maternal education and use of nicotine and alcohol	Maternal-report CBCL	The two groups differed on virtually all CBCL scales (including internalising ($p \leq .001$) and externalising ($p \leq .001$) problem scales), with ME children scoring in the less desirable direction	•Small sample •Wide age range •Retrospective account of drug use •Majority of ME children were Caucasian (85%) •No measure of other drug use or methadone dose

Study	Research design	Developmental domain	Participants	Age(s) at assessment	Retention at last assessment	Poly-drug use during pregnancy	Examination of Confounding Variables	Key outcome measures	Key Findings	Limitations
Soepatmi, 1994	Case control, longitudinal	Behavioural adjustment	1) Opioid exposed group: *n* = 91 No comparison group, results compared to previous research	4-12 years	After one year, 67 (74%) children were followed up	Children were exposed to illicit drugs in-utero, mainly heroin and/or methadone. A subgroup of children were exposed to non-opiates (18.5%)	No	Caregiver-report CBCL	Proportion of children with a total behaviour problem score >90 was significantly larger for boys aged 4-5 years ($p < .001$) and girls aged 6-11 ($p = .012$) exposed to opioids. The proportion of children with a total competence score ≤10 was significantly larger for boys aged 4-5 years ($p = .011$) and girls aged 6-11 years ($p = .0009$)	•No comparison group •High attrition •Significant differences in social risk between lost and retained participants •Not descriptive •No consideration of confounding variables •No measure of methadone dose •No further information on measurement of other drug use
van Baar et al., 1994	Longitudinal	Behavioural adjustment	1) Opioid-exposed group: *n* = 35 2) Comparison children: *n* = 35	4 ½ years & 5 ½ years	10 children had withdrawn at the time of the 5.5 year follow-up	Urine toxicology analysis and self-report revealed 94% of women used combinations of multiple drugs	No	Caregiver-report CBCL	Caregivers reported increased behavioural problems in the opioid-exposed group at age 4.5 years but no behavioural problems at 5.5 years	•Small sample size •High attrition •Poor consideration of confounding factors •No report of methadone dose

Study	Research design	Developmental domain	Participants	Age(s) at assessment	Retention at last assessment	Poly-drug use during pregnancy	Examination of Confounding Variables	Key outcome measures	Key Findings	Limitations
Ornoy et al., 2001	Case control, cross sectional	Behavioural and emotional adjustment	1) Heroin-exposed group raised by parents: *n* = 31 2) Heroin-exposed group adopted: *n* = 34 3) Non-exposed, born to heroin-dependent fathers raised by parents: *n* = 33 4) Non-exposed group, low SES: *n* = 32 5) Non-exposed comparison group: *n* = 30	5-12 years	N/A	Parents with heroin dependency self-reported the use of a variety of substances such as benzodiazepines and cigarettes.	No	•CBCL •Conners Questionnaire	Heroin-exposed children raised by their parents had significantly higher externalising difficulties than control children ($p < .01$) and adopted and low SES children ($p < .05$). Heroin-exposed children had significantly higher internalising difficulties than control children ($p < .01$). Significantly higher proportion of heroin exposed children raised at home obtained clinically significant ADHD symptom scores compared to controls ($p < .01$), adopted and low SES children ($p < .05$), and children raised by addicted fathers ($p < .05$)	•Did not consider confounding effects of poly-drug use in analysis •Maternal self-report of retrospective drug use during pregnancy

Study	Research design	Developmental domain	Participants	Age(s) at assessment	Retention at last assessment	Poly-drug use during pregnancy	Examination of Confounding Variables	Key outcome measures	Key Findings	Limitations
Hunt et al., 2008	Case control, longitudinal	Social adjustment	1) Methadone-exposed group: *n* = 133 2) Non-exposed comparison group: *n* = 103	18 months and 3 years	At the 3-year assessment, 67/133 (50%) of exposed children were retained	Mothers were excluded for other drug use	Mothers were matched for age, height, ethnic background, and obstetric history	Parent-report Vineland Social Maturity Scale	Methadone-exposed children had significantly lower levels of social maturity than non-exposed comparison children at 18-months and 3 years old ($p <$ .05)	•Lack of blind assessors •No report of methadone dose •High attrition •No report of drug use during pregnancy •Did not consider the effect of poly-drug use
Sundelin-Wahlsten & Sarman, 2013	Cross sectional	Behavioural adjustment	1) Buprenorphine-exposed group: *n* = 25 Note: no comparison group, results compared to previous research	5-6 years	N/A	78% of women smoked cigarettes	No	•Parent-report Brown ADD Scales •Parent-report SDQ	SDQ results did not indicate any difficulties on any of the SDQ subscales. Energy, Action, inattention and combination subscales resulted in significantly higher scores than children without ADHD but lower scores than children with ADHD	•No matched comparison group •No further description of poly-drug use •No consideration of confounders •Small sample size

Study	Research design	Developmental domain	Participants	Age(s) at assessment	Retention at last assessment	Poly-drug use during pregnancy	Examination of Confounding Variables	Key outcome measures	Key Findings	Limitations
Konijnenberg et al., 2015	Prospective cohort study	Behavioural and emotional adjustment	1) Methadone-exposed group: *n* = 24 2) Buprenorphine-exposed group: *n* = 11	Approx 4. years	N/A	Mothers used a variety of substances during pregnancy such as tobacco, alcohol, marijuana, amphetamines, benzodiazepine and other opioids	Adjusted for child age, birth weight and maternal education and employment	Caregiver-report CBCL	The maternal risk model accounted for a significant amount of overall variance in internalising (p = .02) and externalising difficulties (p = .02). The combined (maternal risk/teratogenic risk) model also explained a significant amount of the overall variance in internalising (p = .008) and externalising difficulties (p = .003)	•No comparison group •Maternal self-report •Small sample size
Konijnenberg & Melinder, 2015	Prospective cohort study	Behavioural adjustment	1) Methadone-exposed group: *n* = 22 2) Buprenorphine-exposed group: *n* = 9 3)Non-exposed comparison group: *n* = 25	Approx. 4 years	N/A	Mothers who used opioids used a variety of the same substances above (Konijnenberg et al., 2015)	Adjusted for gestational age, birth weight, maternal education and employment	Caregiver-report CBCL	No significant group effects on attention difficulties	•Small sample size •Maternal-report poly-drug use •Higher social risk in exposed children

Study	Research design	Developmental domain	Participants	Age(s) at assessment	Retention at last assessment	Poly-drug use during pregnancy	Examination of Confounding Variables	Key outcome measures	Key Findings	Limitations
Nygaard et al., 2016	Prospective longitudinal	Behavioural adjustment	1) Opioid-exposed group: *n* = 72 2) Comparison group: *n* = 58	4 ½ & 8 ½	26 (20%) children from both groups lost to the 8 ½ follow-up (21% exposed, 19% non-exposed)	Self-report and medical record evidence of tobacco, opiate, alcohol, and benzodiazepines	Adjusted for SES, birth weight, gestational age, time of assessment	•Caregiver-report ADHD Rating Scale •Caregiver-report CBCL	Opioid-exposed scored significantly higher on the ADHD Rating Scale compared to comparison children (p = .004). Significant group differences in externalising problems (p = .05), attention problems (p = .005), and social problems (p = .02)	•Clinical sample •Lack of blind assessors •Small sample size in relation to the no. of analyses •Did not control for other drug use •Comparison group was a convenience sample
Sandtorv et al., 2018	Cross sectional	Opiates	1) Opiate-exposed group: *n* = 57 2) Reference group: *n* = 171	6-14 years	N/A	Exposed to opiates and a range of other illicit substances	Reference children were sex and age matched	Caregiver-report Swanson, Nolan, and Pelham Questionnaire, Revision IV (SNAP-IV)	Caregivers reported significantly higher scores of ADHD symptoms-Combined (p < .001), Inattention (p < .001), and Hyperactivity/ Impulsivity (p <. 001)	•Wide age range •Clinical sample •Unclear extent of poly-drug exposure •Reference children of higher SES •Poor consideration of confounders •No information on drug exposure for reference group

Study	Research design	Developmental domain	Participants	Age(s) at assessment	Retention at last assessment	Poly-drug use during pregnancy	Examination of Confounding Variables	Key outcome measures	Key Findings	Limitations
Azuine et al., 2019	Longitudinal	Mental Health	1) Opioid-exposed group: *n* = 454 2) Comparison group: *n* = 8509	0-6, 6-21	3106 children had medical records available for the first 5 years. 2391 children had medical records available at 6 years and older	Mothers with opioid exposure self-reported heroin (76.7%), oxycodone (44.9%), and methadone use (53.7%). Also self-reported the use of alcohol (16.7%), marijuana (75.1%), stimulants (70.7%), cocaine (66.3%), crack (41.9%), amphetamines (14.5%), ecstasy (32.2%), and PCP (5.9%)	Adjusted for ethnicity, household income, maternal age, maternal education, marital status, low birth weight and preterm birth	ICD-9-CM and ICD-10 codes from medical records	For the first 6 years of life, children exposed to opioids had higher levels of CD/Emotional Disturbance diagnoses compared to non-exposed children (aOR = 2.13). For age 6 and up, children exposed to opioids had higher levels of ADHD diagnoses compared to non-exposed children (aOR = 2.55)	•Clinical sample •Primarily low income minority sample •Did not consider the effect of poly-drug use •Self-reported drug use

Note: ME (Methadone-Exposed); CBCL (Child Behavior Checklist), ADHD (Attention-Deficit Hyperactivity Disorder).

1.5 Methodological Issues in Behavioural and Emotional Adjustment Outcome Studies

Most of the studies on the long-term consequences of prenatal opioid exposure all share common limitations. According to Azuine et al. (2019), there are significant gaps in the knowledge regarding the long-term consequences of maternal opioid use on the child's neurodevelopmental outcomes, as large prospective cohort studies that investigate this issue are limited. Many studies are dated back to the 1970s and 1980s, have relied on maternal-self report measures and have used small sample sizes (Azuine et al., 2019). The more dated studies primarily focused on heroin exposure, followed by methadone (Woodward et al., 2018). Additionally, many studies have an inadequate or no control group, have high rates of attrition, report varying levels of methadone doses, and inadequately control for poly-drug use and other potential environmental/maternal confounding variables. The presence of multiple methodological issues can influence the validity and reliability of the conclusions drawn.

Almost all existing studies are subject to a number of methodological issues. First, the issue of small sample size is prevalent in the previous literature. de Cubas and Field (1993) included 20 methadone-exposed children and 20 non-exposed children in their study. Wilson et al. (1979) included 77 children in their research sample but included only 22 children in the heroin-exposed group. Additionally, Konijnenberg et al. (2015) included 24 methadone-exposed children and 11 buprenorphine-exposed children. Sundelin-Wahlsten and Sarman (2013) included 25 children in the buprenorphine-exposed sample and no comparison group. Small sample sizes can decrease statistical power, therefore creating difficulties with detecting significant associations.

Another significant methodological issue affecting most existing research is the high rate of sample attrition observed over time. For example, Soepatmi (1994) had a retention rate of 43%, with only 67/157 children being followed-up for one year or more. Hunt et al. (2008) retained 59% (n = 79/133) of methadone-exposed children in the 18-month follow-up and only

50% (67/133) of methadone-exposed children in the 3-year follow-up. Retention of participants in drug outcome studies is difficult due to a drug-using lifestyle and culture being associated with social disruption (Hunt et al., 2008). Nygaard et al. (2016) lost 26 children to follow up at 8 ½ years. This can often lead to selective sample loss since those families that were most at risk of being lost to follow-up are likely to be those at greatest risk. For example, Azuine et al. (2019) did not obtain medical records for 47 children in the first six years and did not obtain medical records for 762 children aged six years and above. This could have potentially led to an underestimation of mental health diagnoses in opioid-exposed children. This systematic sample loss and attrition can, in turn, undermine sample representativeness and the interpretation and generalisability of study results. Additionally, and importantly, the loss of study participants can also reduce statistical power.

Some studies did not include an adequate comparison group or did not include one at all (Soepatmi, 1994; Sundelin-Wahlsten & Sarman, 2013). Sundelin-Wahlsten and Sarman (2013) and Soepatmi (1994) referenced results to previous research. Additionally, some studies included comparison groups but did not adequately match them (Konijnenberg & Melinder, 2015). Without an adequate comparison group, it is difficult to determine if the outcomes are due to the prenatal methadone exposure or if they are due to other risk factors. Comparison groups are important to include in a study to help control for validity threats and to extrapolate from the results.

Another important limitation of existing studies examining the long-term outcomes of prenatal methadone exposure is the varying levels of methadone dosages that were administered to women during pregnancy. In addition, many studies did not state the methadone dose levels at all (de Cubas & Field, 1993; Hunt et al., 2008; Soepatmi, 1994; van Baar et al., 1994). Konijnenberg et al (2015) reported an average methadone dose at birth of 85.96mg daily but did not report the range of doses. Due to the differing levels of methadone

dosages, this could result in differing developmental outcomes for the child. Additionally, average methadone doses during pregnancy have increased over the years (Wouldes & Woodward, 2010), which can make it difficult to compare the findings of newer studies to the findings of more dated studies due to different dosage levels.

Some studies gathered maternal drug-use information from maternal self-report measures and structured interviews which could result in validity concerns and potential bias in the responses (Azuine et al., 2019; Konijnenberg et al., 2015; Konijnenberg & Melinder, 2015; Nygaard et al, 2016; Ornoy et al., 2001). For example, de Cubas and Field (1993) gathered poly-substance use information via maternal self-report, however, the measure was not specified any further. The nature of maternal self-report could compromise the accuracy of the results due to systematic biases. Some previous studies have utilised a multi-method approach consisting of maternal self-report, maternal and child clinical records, and toxicological analysis of maternal urine during pregnancy and infant meconium after birth (Hunt, 2008), which assisted in determining important information about the substances used during pregnancy. Under-reporting and under-estimation when utilising self-report measures is also a potential risk factor within the previous research. Some previous studies conducted in countries such as the U.S.A, where there is mandatory reporting of drug use, may have encountered issues with under-reporting on maternal self-report measures of poly-drug use. Due to the criminalization of drug use during pregnancy, this could deter women from reporting their drug use. Additionally, it has been found that people who frequently use drugs tend to under-report the frequency and amount of their substance use compared to occasional drug users, possibly due to stigmatisation concerns or embarrassment (Garg et al., 2016). Additionally, some studies relied on retrospective reports of maternal drug use during pregnancy (de Cubas & Field; Ornoy et al., 2001; Wilson et al., 1979). Retrospective accounts of drug use may result in recall errors.

Results on the long-term outcomes of children who have been born to women who have used opioids while pregnant can be difficult to interpret due to the challenges associated with understanding the impact of other drug exposure and additional environmental factors (Sundelin-Wahlsten & Sarman, 2013). Poly-substance use is common within women dependent on opioids (Jansson et al., 2019). Among previous research, the additional use of alcohol, tobacco, marijuana and other drugs has been commonly reported amongst women who have used opioids during pregnancy. The use of multiple substances is more common than the use of a singular drug in treatment population studies (Jansson et al., 2011). de Cubas and Field (1993) matched the target and control group on alcohol and cigarette use. However, no other studies controlled for poly-drug use during pregnancy. Multiple studies contained uncertainty about the extent of poly-drug exposure (de Cubas & Field, 1993; Sandtorv et al., 2018; Wilson et al., 1979), or did not state the presence of poly-drug use at all (Hunt et al., 2008; Soepatmi, 1994). Azuine et al. (2019) defined substance exposure heterogeneously which included unknown, illicit and therapeutic opioid exposures that lead to a diagnosis of NAS. Due to heterogeneity, long term effects of opioid exposure could be difficult to differentiate, creating uncertainty around the effects of specific opioids (Azuine et al., 2019). Additionally, it remains relatively unknown how maternal multiple drug use during pregnancy in the absence of methadone, or in addition to methadone affects the developing child (Jansson et al., 2011).

Lastly, a major limitation in the published research on the emotional and behavioural outcomes of children prenatally exposed to opioids is the lack of consideration of environmental factors that may also influence development. Common maternal and family risk factors that are correlated with maternal opioid use include mental health issues, family violence, poverty, lack of social support and low socioeconomic status (Nygaard et al., 2016). These factors have also been found to contribute to behavioural and emotional adjustment difficulties in children. Alluding to the consideration of confounding variables, some studies

included multiple groups of differing environments to attempt to disentangle the effects of the substance and the pre/postnatal environment (Ornoy et al., 2001; Wilson et al., 1979). Some studies also matched their participants on various factors to attempt to control for confounding variables (de Cubas & Field, 1993; Hunt, 2008; Sandtorv et al., 2018; Wilson et al., 1979). However, numerous studies have not adequately controlled for confounding environmental/maternal factors and the use of multiple substances in their statistical analyses (de Cubas & Field, 1993; Soepatmi, 1994; Sundelin-Wahlsten & Sarman, 2013; van Baar et al., 1994). This is important because it makes the relationship between drug exposure and the observed outcomes unclear, as disentangling the effects of prenatal methadone exposure and the effects of environmental factors can be difficult. Without adequate controlling of confounding factors, group differences can be subject to overestimation. Some studies controlled for various confounding factors in their analysis (Azuine et al, 2019; Konijnenberg & Melinder, 2015; Nygaard et al, 2016; Wilson et al., 1979). Although these studies had adjusted for various socio-familial/infant factors, they did not control for poly-drug use during pregnancy. These studies were mainly published in recent years compared to the remaining studies that did not consider confounding variables.

1.6 Conceptual Framework

As foetal neuroanatomical growth is occurring in-utero, drug exposure may disturb specific events in brain development (Woodward et al., 2018). In-utero exposure to drugs can have long-term implications for the child's neurological functioning and structure (Ross et al., 2015). Approximately two weeks after conception, the human brain starts to develop (Bick & Nelson, 2016). During the prenatal period, the central nervous system undergoes multiple developmental processes. These processes include neural induction, neurulation, proliferation, migration, axonal outgrowth and synaptogenesis, differentiation and apoptosis (Monk, Webb,

& Nelson, 2001). Therefore, this period of neurological development is a particularly vulnerable period for the developing foetus. Prenatal exposure to substances during this sensitive period of brain development can have both direct and indirect effects on the foetal brain and may disrupt the developmental trajectory. Substances can directly affect the developing foetus through placental transfer and indirectly through the alteration of maternal physiology (Szeto, 1995). Lifestyle factors that may accompany mothers who use drugs during pregnancy can also increase the child's vulnerability to adverse outcomes.

1.6.1 Direct Pathway

Prenatal opioid exposure can directly influence neurodevelopment in-utero. The direct pathway refers to the distribution of opiates across the placenta to the developing foetus (Szeto, 1995). Essentially, the substance crosses the placenta and directly affects the development of the foetus. Direct effects of drug exposure on the developing brain vary according to the timing of exposure during gestation, drug type, polypharmacy, the extent of drug distribution and dosage level (Woodward et al., 2018). The stage of foetal development, as well as the sensitivity of the nervous system and different brain regions to different teratogens, may also influence the trajectory of brain development (Woodward et al., 2018).

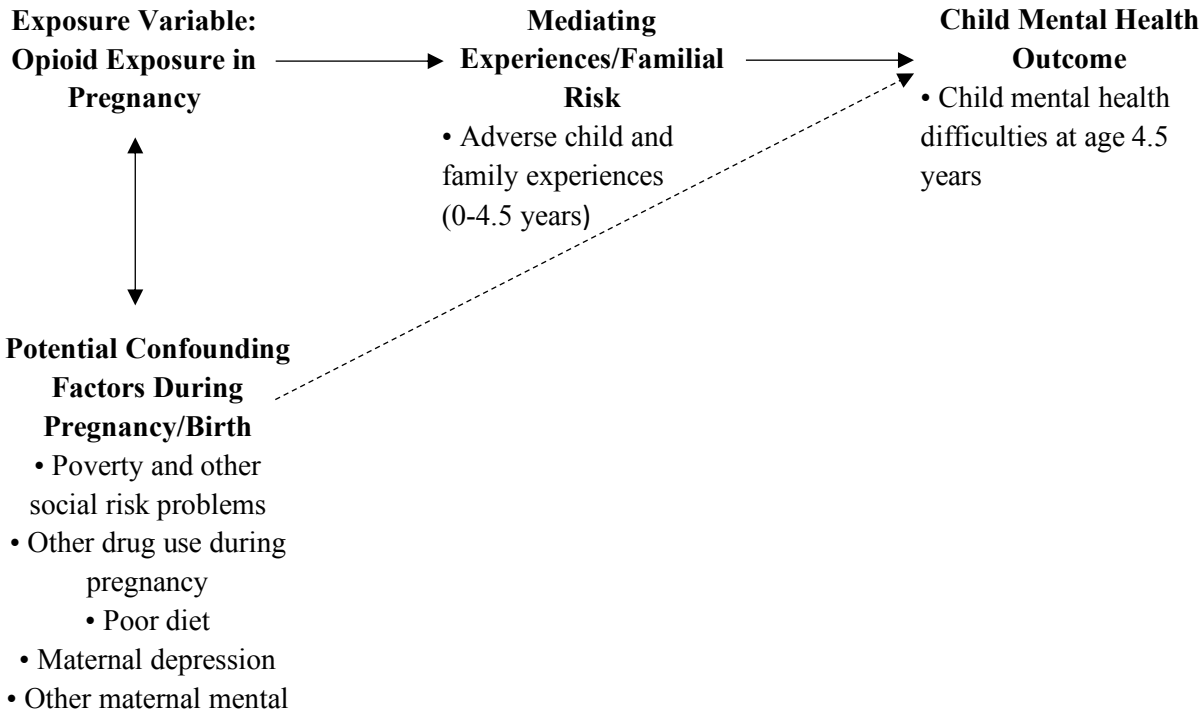
1.6.2 Indirect Pathway

In addition to the direct effects of prenatal opioid exposure on foetal/infant brain development and behaviour, opioids can indirectly affect foetal neurodevelopment through the impact on other physiological systems (Woodward et al., 2018). Opioids can alter maternal-placental physiology (Szeto, 1995). Adverse outcomes after prenatal opioid exposure can be secondary to alterations in maternal physiology (Ross et al., 2015; Szeto, 1995), and exposure can compromise the delivery of substrates and oxygen to the foetus (Szeto, 1995). Since many different types of drugs can impact nutritional exposure and foetal blood flow (Woodward et

al., 2018), the occurrence of poly-drug use can make it difficult to determine the indirect effects of each drug. The indirect pathway also includes the influence of other environmental and maternal lifestyle factors on the developing child. Increased mental health behaviours caused by addiction and increased production of stress hormones are examples of maternal physiological characteristics that can secondarily alter foetal development (Ross et al., 2015). Children who have been prenatally exposed to methadone are often exposed to the effects of maternal emotion dysregulation and psychopathology, problematic maternal interactions, and poverty (Hans & Jeremy, 2001). Additionally, high levels of early psychosocial stress can influence foetal development, with findings suggesting that prenatal stress can exert programming effects on the stress response and neuroendocrine systems (Conradt, Crowell, & Lester, 2018). Developmental outcomes such as behavioural and emotional maladjustment in opioid-exposed children are likely the result of both biological and environmental risk factors. Figure 1 illustrates the complex interplay of factors and processes that can contribute to early-onset mental health disorders in ME preschool children.

Figure 1

Model of Potential Factors Involved in the Mental Health Outcomes of Methadone-Exposed Young Children



1.6.3 Neurosequential Model

The Neurosequential Model, a sequentially-organising functional model of the brain, provides a useful framework for mapping the neurological development of children exposed to prenatal and postnatal trauma (Hambrick, Brawner, & Perry, 2019). Adverse experiences such as prenatal exposure to drugs can influence the developing brain and can disrupt a typical trajectory of neurodevelopment, resulting in atypical patterns of neurohormonal and neural activity (Perry, 2009). According to this model, the brain is organised hierarchically, with the lower parts of the brain mediating basic regulatory functions and the higher parts of the brain mediating complex functions such as abstract thinking (Perry & Hambrick, 2008). The lower sections of the brain are the first to develop, as the brain develops in a bottom-up sequence. The limbic system, located above the brainstem and below the cerebral cortex, controls functions such as affect, relational functioning and attunement (Perry, 2013). The brain

continues to grow and organise itself, proceeding up through to the complex sections of the brain (Perry, 2006).

Intrauterine insults can affect norepinephrine, dopamine and serotonin systems of the brainstem and diencephalon, which undergo rapid organisation during the early years of life (Perry & Hambrick, 2008). Brainstem and diencephalon development is related to issues with attention, impulsivity and self-regulation (Perry, 2009). If the lower sections of the brain that are responsible for stress response systems are disrupted by intrauterine insults during development, disorganisation and dysregulation of the higher regions of the brain can occur (Perry, 2006). This can lead to observed difficulties in various areas of functioning, including behavioural and emotional regulation. Additionally, various studies have reported significant difficulties in cognitive and motor functioning for opioid-exposed children, which further demonstrates the cascade effect of intrauterine trauma. Therefore, such impairment in brain development may function as a potential causal mechanism contributing to behavioural and emotional maladjustment that can be observed in ME children. Postnatal adverse experiences such as attachment disruptions and traumatic stress can also disrupt typical brain development. This can result in a cascade of neurodevelopmental outcomes such as behavioural, social and emotional dysregulation and impaired speech and motor functioning (Perry, 2009). Since children born to methadone-maintained mothers are likely to be born into high social risk contexts, this may increase their risk of adverse postnatal experiences that may influence neurodevelopment.

1.7 Socio-Familial Factors

It is important to note some of the significant maternal and socio-familial risk factors that can contribute to the relationship between prenatal methadone exposure and later behavioural and emotional adjustment in preschool children. Although MMT for pregnant women utilises a harm-reduction approach and can be less harmful than illicit and uncontrolled

drug use for both the mother and developing foetus, multiple risk factors can be concurrent with MMT. In comparison to the general population, women enrolled in MMT have been found to have increased levels of adverse birth and maternal outcomes (Davie-Gray, Moor, Spencer, & Woodward, 2013; Patrick, Schumacher, Benneyworth, Krans, McAllister, & Davis, 2012).

Maternal psychopathology is a significant predictor of later behavioural and emotional adjustment in children and is highly correlated with MMT during pregnancy. In the same cohort as the present study, Davie-Gray et al. (2013) found that 43% of MMT women experienced depressive symptoms that met criteria for probable clinical depression and had high levels of poly-drug use during pregnancy (Davie-Gray et al., 2013). Approximately 12% of MMT women were taking prescribed benzodiazepines and 3.7% of MMT women were using prescribed antipsychotic medication during pregnancy, compared to no comparison women (Davie-Gray et al., 2013). These findings represent the level of comorbidity between substance dependence and psychiatric disorder in methadone-maintained (MM) women (Davie-Gray et al., 2013). Children with mothers who are depressed and/or anxious are at a higher risk of an array of behavioural outcomes such as withdrawal, antisocial behaviour, acting out, and further psychiatric and emotional issues (Najman, Bor, Andersen, O'Callaghan, & Williams, 2000).

Other biological factors that can influence the development of behavioural outcomes include child sex and maternal nutrition during pregnancy. Sex differences in the prevalence and presentation of behavioural and emotional adjustment difficulties have been observed. Specifically, boys are diagnosed with ADHD at a higher frequency compared to girls at a ratio of 2:1 (American Psychiatric Association, 2013). Both ODD and CD are reportedly more prevalent in boys (Maughan, Rowe, Messer, Goodman, & Meltzer, 2004). Additionally, the lack of prenatal exposure to sufficient nutrients may also affect neurodevelopment in-utero and may lead to the child exhibiting behavioural problems. Women enrolled in MMT during

pregnancy may be at an increased risk of having a poor diet during pregnancy (Levine and Woodward, 2018; Tomedi, Bogen, Hanusa, Wisner, & Bodnar, 2012). A weak but robust association between better maternal diet and lesser behavioural problems in the child has been reported (Borge, Aase, Brantsaeter, & Biele, 2017). Although the association is not strong, this suggests there may be a relationship between maternal nutrition during pregnancy and neurodevelopmental outcome.

As evidenced in the previous literature review, women enrolled in opioid maintenance treatment programs are likely to be using multiple other drugs during pregnancy, such as marijuana, benzodiazepines, tobacco, alcohol and amphetamines (Konijnenberg et al., 2015; Levine & Woodward, 2018). The use of multiple drugs during pregnancy in addition to methadone negatively influence neurodevelopment and subsequently could lead to behavioural and emotional issues later in life. The interactive or additive effect of multiple substances may result in outcomes that differ from the effect of solely opioids (Larson et al., 2019).

A variety of social risk factors have been linked to the development of externalising behaviour problems in preschool children. Davie-Gray et al. (2013) investigated the characteristics of pregnant women receiving MMT and found mothers enrolled in MMT had significantly higher levels of psychosocial and maternal risk factors compared to non-exposed comparison women. Methadone-maintained women had significantly higher levels of social adversity during pregnancy, such as welfare dependency, no formal qualifications and were less likely to be in a stable relationship (Davie-Gray et al., 2013). Burke, Loeber, and Birmaher (2002) noted several socioeconomic factors associated with disruptive behaviour amongst children, such as parental unemployment and low SES. Children from families of lower SES are at an increased risk of behavioural adjustment difficulties (Hosokawa & Katsura, 2018; Loeber, Burke, Lahey, Winters, & Zera, 2000; Najman et al., 2000). Low SES is also correlated with factors such as early maternal pregnancy and parental psychopathology (Najman et al.,

2000). A combination of socio-familial factors such as the factors discussed may heighten the risk of poor neurodevelopmental outcomes in opioid-exposed children.

1.8 Study Aims

The overall aim of this thesis was to assess the extent to which children exposed prenatally to methadone might be at increased risk of experiencing a range of early-onset psychiatric disorders that are relatively rare in younger children. Disorders examined spanned both clinically significant externalising and internalising problems and disorders, including rates of DSM-IV diagnoses of Oppositional Defiant Disorder (ODD), Attention-Deficit Hyperactivity Disorder (ADHD), Conduct Disorder (CD), Anxiety Disorders, Depression and Autism Spectrum Disorder (ASD). Previous research based primarily on parent-report shows that children exposed prenatally to opioids are found to have higher levels of hyperactivity, attention problems and impulsivity (Nygaard et al., 2016; Ornoy et al., 2001; Sandtorv et al., 2018; Sundelin-Wahlsten & Sarman, 2013), as well as other externalising behaviour difficulties such as conduct problems (Azuine et al., 2019) and social difficulties (de Cubas & Field, 1993; Hunt et al., 2008; Nygaard et al., 2016; Soepatmi, 1994). Although there is less evidence for internalising difficulties, some studies have reported increased levels of depressed mood and anxiety in opioid-exposed children (de Cubas & Field, 1993; Ornoy et al., 2001). However, little is known about the extent to which these children are at risk of later meeting DSM-IV criteria for mental health or psychiatric disorder, or how these difficulties may present at an early age. Therefore, the specific aims of this thesis were as follows.

1. To examine the extent of parent-reported behavioural and emotional difficulties at age 4.5 years in a cohort of children who were prenatally exposed to methadone compared to a regionally representative sample of non-exposed comparison children. A range of

child behavioural and emotional adjustment problems were measured using the parent-completed Strengths and Difficulties Questionnaire (SDQ).

2. To assess the extent to which 4.5-year-old ME children were subject to a DSM-IV psychiatric disorder relative to non-exposed comparison children. The risk of externalising and internalising disorder diagnoses was measured using the Development and Well-Being Assessment (DAWBA), with diagnoses assigned by a registered clinical psychologist (SA) for all children.
3. Assess the extent and patterns of psychiatric comorbidity in children prenatally exposed to methadone. That is, the degree to which children in each group might meet the criteria for two or more psychiatric disorders and the nature of these comorbidities.
4. Examine the extent to which observed associations between prenatal methadone exposure and later psychiatric risk might be explained by confounding factors correlated with maternal methadone use during pregnancy. Confounding factors were identified based on previous research and theory and included maternal psychiatric illness during pregnancy, social risk, child sex, birth weight, maternal poly-drug use during pregnancy and prenatal maternal nutrition.

2. METHOD

2.1 Research Design

This study draws on quantitative data from a prospective longitudinal study, the Canterbury Methadone in Pregnancy (MIP) study. The overall goal of the MIP study is to understand the developmental outcomes of children born to mothers maintained on methadone during pregnancy. The data that will be used in this sub-analysis were collected at age 4.5 years as part of a comprehensive child neurodevelopmental assessment at the Canterbury Child Development Research House, located on campus at the University of Canterbury, Christchurch. Prior to the 4.5-year- assessment wave, data on both ME and NE comparison children were collected at three separate time points (birth, 18 and 24 months).

Around the time of birth, detailed information about each mother's personal, social and pregnancy background was collected as part of an extensive interview conducted by a senior neonatal research nurse. This information was combined with data from maternal and infant medical records, in addition to a toxicological analysis of maternal urine samples during pregnancy and infant meconium analysis after birth.

At the 18-month assessment, parent-child interaction observations were recorded and measures of familial circumstances and other psychosocial characteristics were administered during the maternal interview. This home visit was then followed six months later with a clinic-based neurodevelopmental evaluation when children turned two years old.

The 4.5-year evaluation assessed various aspects of familial/maternal circumstances and child neurodevelopment. The present study focuses on two key measures of behavioural and emotional adjustment that were administered as part of the 4.5-year follow-up interview with each study child's primary caregiver. Provided below is a description of the present study sample, procedure, key outcome and other measures, and the data analysis plan.

2.2 Study Sample

The study sample comprised two groups of 4.5-year-old children who were born at Christchurch Women's Hospital (n = 190). All mothers were recruited during pregnancy or at birth from Christchurch Women's Hospital between 2003 and 2008. Exclusion criteria for both groups of children included an HIV positive diagnosis, a diagnosis of Foetal Alcohol Syndrome (FAS), very preterm birth (≤32 weeks), congenital abnormalities, and non-English speaking parents. Children with severe Autism and developmental delays were also excluded from the study.

2.2.1 Methadone-Exposed Group

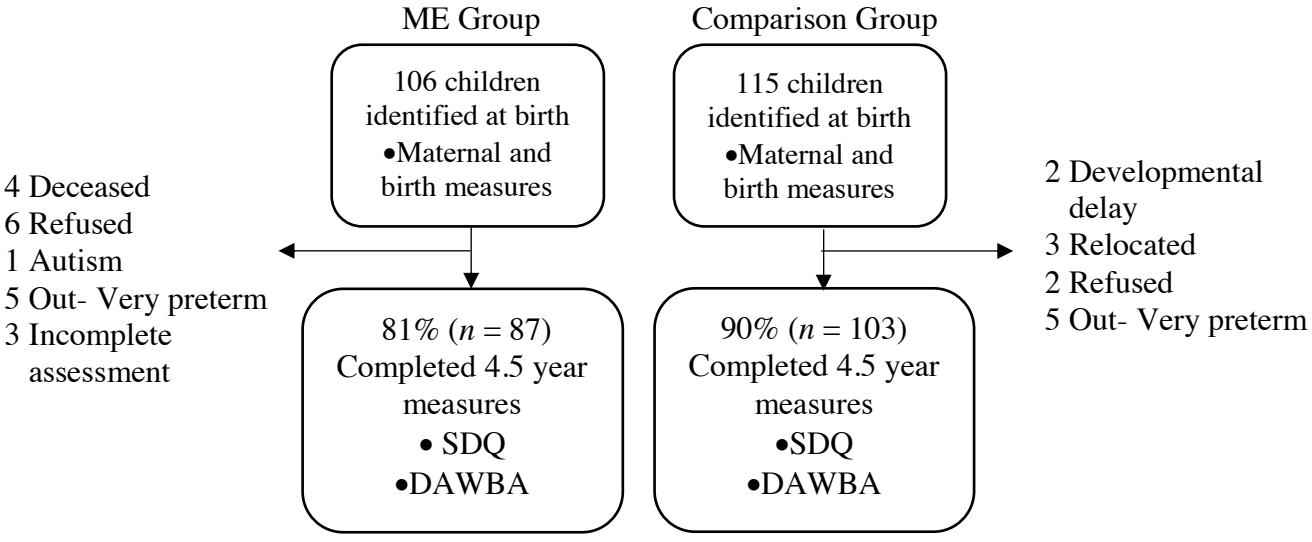
The first group, the methadone-exposed group (ME) (45.8% of the sample), consisted of 87 children born to mothers enrolled in the Christchurch Methadone Programme during pregnancy from 2003 to 2008. The Christchurch Methadone Programme works in partnership with the antenatal obstetric team at Christchurch Women's Hospital. This service includes access to Methadone Maintenance Treatment and antenatal support for women dependent on opioids during pregnancy. At birth, 106 ME infants were initially identified. To be included in this study, women in the ME group were required to be enrolled in MMT during pregnancy and meet the above inclusion criteria. At the time of the 4.5-year assessment, 19 children had died or been lost to follow-up. Figure 2 presents the study design and the reasons for sample attrition at the time of the 4.5-year assessment. A total of 86 mothers with 87 children (one set of twins) completed parental/primary caregiver interview and were included in this analysis (81%). The ME child group included 51 males (58.6%) and 36 females (41.4%). Information about the maternal daily methadone administration during pregnancy was obtained via hospital and drug service records. The average methadone treatment dose for women during their third pregnancy trimester approximately 65mg/day (SD = 32.65; range = 0-195mg/day).

2.2.2 Non-Exposed Comparison Group

The second group, referred to as the non-exposed comparison group, consisted of 103 non-methadone exposed children aged 4.5 years old (54.2% of the sample). Non-exposed children were born to women who were randomly identified from the Christchurch Women's Hospital delivery booking schedule and were then invited to participate in the initial parent interview at or close to the birth of their infant/s. The women included in the comparison group were representative of pregnant women in the Canterbury region, according to comparisons of the socioeconomic profile to regional census data. At birth, 115 comparison infants were initially identified. Twelve children did not participate in the 4.5-year follow-up, resulting in 103 comparison children completing the follow-up assessment (90%). Reasons for attrition are presented in Figure 2. The comparison group included 45 males (43.7%) and 58 females (56.3%).

Figure 2

Overview of Study Design



2.3 Procedure

Mothers were contacted in person or by telephone when their child was as close as possible to age 4.5 years old and invited to participate in a follow-up child developmental evaluation. Each mother who participated in this study provided informed consent. Each evaluation consisted of one developmental assessment session at the Canterbury Child Development Research House, which took approximately four hours. Child assessment measures were selected to provide a comprehensive descriptive evaluation of children's mental health, neuropsychological and motor development, in addition to each child's caregiving environment. Breaks were provided as needed, and if necessary, completed across two sessions. All measures were administered by appropriately trained research staff and students with postgraduate or professional qualifications. The trained clinical psychologist who assigned diagnoses was blind to group membership. Research staff/students received training and were regularly supervised by the study principal investigator (LW) in the administration of all assessment procedures.

2.4 Ethics Approval

Ethics approval for this study was obtained from the Canterbury Regional Ethics Committee (Ethics Ref: URB07/10/042). Informed, written consent was obtained from all mothers participating in the study (see Appendix C).

2.5 Measures

As part of a structured parent interview, a series of standardised questionnaire measures were administered, including the parent-report screening Strengths and Difficulties Questionnaire (SDQ). Following the completion of the SDQ, the DAWBA interview was administered during the interview. Custom written questions were included in the parental interview where needed. The parental interview required about 45-60 minutes and was

administered by the study coordinator who was a trained research nurse. The interview was completed in a private room adjacent to where their child was being tested. A video link was available between the two rooms so the parent could view their child at all times. The following key measures from this assessment were included in this analysis.

2.5.1 The Strengths and Difficulties Questionnaire (SDQ)

The SDQ is a widely used screening tool that consists of 5 subscales assessing the extent of conduct problems, hyperactivity/inattention, emotional symptoms, peer problems, and prosociality in children and youth aged 3-16 years old (Goodman, 2001). In the present study, the SDQ was utilised to provide a measure of parent-reported behavioural and emotional adjustment (see Appendix A). Parents, teachers and youth themselves can complete the questionnaire. The SDQ consists of 25 items that are rated on a 3-point Likert scale ranging from 0 "not true" to 2 "certainly true" (Goodman, 1997). Higher scores indicate increased difficulties for the conduct, hyperactivity/inattention, emotional symptoms and peer problems subscales, whereas lower scores on the prosocial subscale indicate difficulties with prosocial behaviour. Additionally, five items are presented as strengths and are then reverse-scored as problems.

Items included in the SDQ measure both positive and negative attributes of the child (Goodman, 2001). The conduct problems subscale includes items such as "Often has temper tantrums or hot tempers" and "Often fights with other children or bullies them". Items regarding non-compliance, lying and cheating, and stealing are also included within this subscale. The hyperactivity/inattention subscale focuses on inattentiveness, hyperactivity, and impulsiveness, with items such as "easily distracted, attention wanders" and "thinks things out before acting". The emotional symptoms scale focuses on internalising difficulties, with items such as "many worries, often seems worried" and "many fears, easily scared". Difficulties with peers are indicated by higher scores on items such as "picked on or bullied by other children"

and "rather solitary, tends to play alone". Lastly, the prosocial scale includes items that indicate prosocial behaviours such as consideration of others and sharing.

The groupings of selected SDQ items into subscales was based on diagnostic classifications and factor analyses (Goodman, 2001). Items for each subscale can be summed to create a scale score ranging from 0-10 (Goodman, 1997). A total difficulties score ranging from 0-40 can be computed by summing the children's scores on the conduct problems, hyperactivity/inattention, emotional symptoms and peer problems subscales (Goodman, 1997), giving an indication of the children's overall behavioural and emotional adjustment. The prosocial scale is not included in the total difficulties score as it is weakly associated with the risk of psychiatric disorder (Goodman, 2001). An impact supplement is included in extended versions of the SDQ. The impact supplement asks the respondent if they believe the child has significant difficulties, and if the respondent answers yes, they are asked further questions about the timeframe, child's distress, impairment and burden (Goodman & Scott, 1999).

SDQ bandings can organise children's scores on each subscale as normal, borderline and abnormal (Kersten et al., 2016). The use of cut-points can identify children that fall within the clinically significant range. Impairment was defined utilising the most severe 10% cut-point on each of the subscales and total difficulties score. In the present study, clinical cut-off variables were created for each subscale and the total difficulties score based on the 10% of comparison children with the most severe difficulties. This was done because of the availability of a comparison group and due to the young age of study children relative to the sample on which test norms were established. This is a well-accepted approach in the paediatric literature (Delobel-Ayoub et al., 2006; Woodward et al., 2009). On each subscale, a score equal to or greater than the 90th percentile indicated abnormal difficulties (conduct problems ≥3, hyperactivity/inattention ≥6, emotional problems ≥4, peer problems ≥3, prosociality ≤6, and total difficulties ≥11). SDQ scores within the severe top 10% have been associated with an

increased risk of psychiatric difficulties, and each subscale has been associated with the relevant DSM-IV diagnoses (Goodman, 2001)

The SDQ is a highly popular and accessible measure of child behavioural and emotional difficulties. There are multiple versions in different languages, which are used across many countries and populations (Palmieri & Smith, 2007). The SDQ is also available online and is free of charge (Palmieri & Smith, 2007). Additionally, the psychometric properties of the SDQ have been extensively tested across a variety of settings (Vostanis, 2006).

Reliability of the SDQ has been shown to vary. A meta-analytic review by Stone, Otten, Engels, Vermulst, and Janssens (2010) reported weighted mean internal consistency results from 26 studies on the parent-report SDQ, with hyperactivity/inattention having an internal consistency of 0.76, and the rest of the subscales having an internal consistency less than 0.70. The total difficulties and impact scores had an internal consistency above 0.80. In contrast, Croft, Stride, Maughan, and Rowe (2015) reported good internal consistency across the SDQ subscales administered to preschool children. Stone et al. (2010) also measured the test-retest reliability of the parent-report SDQ and reported average to levels of reliability over time. Although the internal consistency and test-retest reliability vary between subscales and studies, the reliability of the SDQ is satisfactory.

An important aspect of the SDQ is its ability to strongly correlate with similar measures of child behaviour and emotional difficulties. The SDQ has been shown to highly correlate with the well-established Rutter Scale (Goodman, 1997), and the CBCL (Goodman & Scott, 1999), suggesting the SDQ has good concurrent validity. In a systematic review by Kersten et al. (2016), most studies reported adequate specificity of the SDQ (>70%) and inadequate sensitivity (<70%), suggesting that some children with significant difficulties may be missed. However, studies have reported good discriminative validity of the SDQ in a range of

populations, including low and high-risk children and other populations that are hypothesised to have different scores (Goodman & Scott, 1999; Kersten et al., 2016).

2.5.2 The Development and Well-Being Assessment (DAWBA)

The Development and Well-Being Assessment (DAWBA) is a semi-structured interview that provides DSM-IV and ICD-10 mental health diagnoses in children aged 2-17 years (Goodman, Ford, Richards, Gatward, & Meltzer, 2000). The DAWBA was designed for a nationwide survey on a large sample of British children and adolescents, investigating common behavioural and emotional disorders (Goodman et al., 2000). In the present study, a trained interviewer administered the DAWBA to parents during the parental interview. Information from parents is then subsequently combined with teacher report and other clinical data to comprehensively assess the child's difficulties in multiple settings and from a range of perspectives.

The DAWBA assesses a range of child psychiatric diagnoses, which are assigned by experienced clinicians after reviewing the data. The key diagnoses generated by the DAWBA that were of interest in the present study were externalising disorders (ADHD, ODD, and CD) and internalising disorders (Major Depressive Disorder, Generalised Anxiety Disorder, Separation Anxiety Disorder, Specific Phobia, and Social Phobia). When administering the DAWBA, the interviewer asks parents about the symptoms and criteria required for a DSM-IV or ICD-10 diagnosis (see Appendix B). This includes the significant impact and impairment associated with the symptoms, which is necessary for a psychiatric diagnosis. According to the "skip rule", the interviewer can skip the questions in a section unless enough of the initial screening questions are positive (Goodman et al., 2000). If positive, the parent is asked structured questions about the symptoms, which is supplemented by further semi-structured information about the child's difficulties in the parent's own words (Goodman et al., 2000). Responses to the interviews and questionnaires are then entered into a computerised diagnostic

algorithm which predicts the probability of having a DSM-IV/ICD-10 diagnosis (www.dawba.net). The computer prediction assigns probability bands to each child, which range from 0.1% to >70%, representing the probability of having a psychiatric diagnosis/diagnoses. After reviewing the provisional computer-generated diagnosis, a qualified clinician would decide whether to accept or reject the risk of disorder based on additional data gathered on each child, which included information from the parental interview. Therefore, the final diagnostic decision was made by the clinician.

Strengths of the DAWBA in clinical work include its mixture of open-ended and structured questions which means that the descriptions of the respondent's problems in their own words can be reviewed (Aebi, Kuhn, Metzke, Stringaris, Goodman, & Steinhausen, 2012). Additionally, all major DSM-IV diagnoses are covered, as well as coexisting diagnoses that could be missed during the interview (Aebi et al., 2012). Finally, the DAWBA can be conveniently administered over the internet (Aebi et al., 2012).

In terms of reliability, less research has been published on the inter-rater and test-retest reliability, as most research has focused on validity. Aebi et al. (2012) conducted a randomised trial of the DAWBA in a clinical sample and noted satisfactory inter-rater reliability of both internalising and externalising disorder diagnoses, suggesting that there is substantial agreement amongst clinical interviewers.

Goodman et al. (2000) provided evidence that supports the validity of the DAWBA. Compared to the community sample, there were significantly higher psychiatric disorder rates in the clinic sample (Goodman et al., 2000). Goodman et al. (2000) reported approximately 89% specificity in the community sample and 92% sensitivity in the clinical sample of children. Within the community sample, children with and without DAWBA diagnoses differed on independent measures of external characteristics (Goodman et al., 2000). Additionally, within

the clinical sample, DAWBA diagnoses were in agreement with the children's clinical case notes, suggesting the DAWBA compares well to other forms of psychiatric assessment.

2.5.3 Measures of Confounding Maternal and Birth Characteristics

As noted previously, a maternal interview was administered during pregnancy or at birth to gather information about each woman's familial circumstances and personal background, as well as maternal substance use, mental health and nutrition (copy of maternal interview available on request). Data on infant characteristics such as sex and birth weight were also recorded from hospital records.

Maternal Social Risk at Birth

For data reduction purposes, a composite measure of maternal social risk was created by summing five dichotomously scored maternal social factors. These five dichotomous social risk factors included early maternal age (1= < 21 at the time of birth), minority ethnicity (1= Māori, Pacific Islander, Asian or African), low maternal education level, single parenthood, and family SES. SES was measured using the Elley-Irving Socio-Economic Index, which classified families as low SES if they were unemployed or working unskilled, semi-skilled, or skilled jobs. Families were classified as high SES if they were working managerial, technical, or professional jobs.

Maternal Substance Use During Pregnancy

The use of substances such as alcohol, cigarettes, cannabis, benzodiazepines, stimulants, and other opiates (other than prescribed methadone) was recorded via maternal self-report, random maternal urine toxicology analysis during pregnancy and infant meconium samples at birth. The use of self-report measures of substance use as well as analysis of maternal urine and infant meconium helped to verify the accuracy of self-reported drug use. Maternal wellbeing was also assessed in the maternal interview.

Maternal Depression Symptoms During Pregnancy and at Birth

Maternal depression was measured using the Edinburgh Postnatal Depression Scale (Cox, Holden, & Sagovsky, 1987). Mothers were also asked if they had been treated for any psychiatric illness during pregnancy.

A series of questions related to nutrition during pregnancy was also included in the interview, such as the average total weekly servings of vegetables, meat, fruit, eggs, bread, milk and cereals.

2.6 Data analysis

The data in this study were analysed using SPSS Statistics Version 25. The $p < .05$ significance level was used to detect statistical significance. The analysis was done in three steps. First, between-group differences in the child and family characteristics of the two study groups were compared using independent samples t-tests for continuous variables or the chi-squared statistic for dichotomous variables. Second, between-group differences in the behavioural and emotional outcomes of study children as measured using the SDQ and DAWBA were assessed using similar statistical methods. Depending on the distributional properties of the outcome variable of interest, Cohen's *d* or the Odds Ratio will be used to provide a measure of the effect size of the extent of the difference in means between the two groups. The third step in the analysis examined the extent to which significant relationships between prenatal methadone exposure and children's later mental health outcomes reflected a) the direct effects of methadone exposure during pregnancy and/or b) the effects of confounding maternal and other adverse pregnancy factors correlated with maternal methadone treatment during pregnancy. A wide range of possible confounders was considered. These were identified from previous literature on factors correlated with MMT during pregnancy and child adjustment outcome, as well as an examination of their relationship with prenatal methadone exposure in the present study, as shown in Table 2. These analyses involved the use of multiple regression analysis to investigate whether methadone exposure during pregnancy continued to

predict the psychiatric outcomes of children at 4.5 years, even after significant confounding factors were statistically controlled for. Since the dependent variables in this analysis were dichotomous, a binary logistic regression was performed.

3. RESULTS

3.1 Sample Characteristics

3.1.1 Maternal Social Background and Pregnancy Characteristics

Table 2 describes the social background and pregnancy characteristics of mothers in the two study groups. Significant between group differences were found across all maternal variables, except for rates of young motherhood < 21 years of age (p = .63). Specifically, methadone-maintained mothers were younger at birth (p = .01) and were more likely than comparison mothers to be a single mother (p < .0001). They were also more likely to have no educational qualifications (p < .0001) and living in low SES circumstances (p < .0001). During pregnancy, MM mothers had higher rates of psychiatric illness (p < .0001), more symptoms of depression based on their EPDS scores (p < .0001), and had a lower quality food diet (p < .0001) during pregnancy. These findings suggest women enrolled in MMT during pregnancy were obstetrically and socially a high-risk population.

Table 2

Characteristics of Mothers Maintained on Methadone and Comparison Mothers

Pregnancy Characteristics	MM (n = 87)	Comparison (n = 103)	$t/\chi 2$	p
M (SD) Maternal Age	29.81 (5.34)	31.75 (5.33)	-2.50	.01
% Young Mother <21 years	3.4	4.9	.23	.63
% No School Qualification	80.5	19.4	70.49	< .0001
% Single Mother	49.4	9.7	36.99	< .0001
% Low SES	94.3	25.2	91.56	< .0001

% Any Psychiatric Illness	57.0	16.7	33.28	< .0001
% Positive EPDS Score ≥ 13	61.2	12.6	48.54	< .0001
M (SD) Nutrition Score	56.6 (20.9)	90.8 (25.4)	-10.21	< .0001

Table 3 examines the ethnicity of MM mothers and comparison mothers. As shown, the ethnic profile of the two groups differed significantly (p = .01). Specifically, the majority of mothers' in both study groups self-identified as of NZ European/other European descent (77% and 81.6%, respectively). The ethnic backgrounds of mothers in the comparison group were more ethnically diverse than the methadone in pregnancy group, however, there were more Māori mothers in the MM group compared to the comparison group (23% and 10.7%, respectively). Approximately one quarter of MM mothers were of Māori descent compared to 10.7% of comparison mothers. A small proportion of comparison mothers were of Pacific Islands ethnicity and approximately 7% of comparison mothers were of "other" ethnicity, predominantly of Asian/African descent. No MM mothers self-identified within these two categories.

Table 3

Ethnicities of Mothers Maintained on Methadone and Comparison Mothers

Maternal Ethnicity	MM (n = 87) (%)	Comparison (n = 103) (%)
New Zealand European/Other European	77.0	81.6
Maori	23.0	10.7
Pacific Islander	0.0	1.0
Other	0.0	6.8

Note: $\chi 2 = 11.26$ (3); p = .01

3.1.2 Substance Use During Pregnancy

The use of other licit and illicit drugs besides methadone during pregnancy was also carefully documented. As shown in Table 4, mothers maintained on methadone had significantly higher rates of both licit and illicit drug use during pregnancy compared to comparison mothers. This was observed for all drugs excluding alcohol use during pregnancy, which did not differ significantly between MM mothers (17.2%) and comparison mothers (20.4%). In contrast, there was a large difference between MM mothers' cigarette use during pregnancy (92%) compared to comparison mothers' cigarette use during pregnancy (15.5%). Methadone-maintained mothers also smoked more cigarettes each day compared to comparison mothers ($p < .0001$). In terms of prescribed drugs, 13.8% of MM mothers used prescribed benzodiazepines during pregnancy, compared to no comparison mothers ($p < .0001$). Finally, no significant between group differences were found in the use of prescribed Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants during pregnancy ($p = .29$).

Table 4

Rates of Poly-Substance Use in Mothers Maintained on Methadone and Comparison Mothers

Maternal Drug Use During Pregnancy	MM Mothers ($n = 87$)	Comparison Mothers ($n = 103$)	$\chi 2$	p
(%) Alcohol	17.2	20.4	.30	.58
(%) Cigarettes	92.0	15.5	110.19	<.0001
M(SD) Daily cigarette use across pregnancy	13.02	1.42	11.08	<.0001
(%) Cannabis	48.3	1.0	60.28	<.0001
(%) Illicit benzodiazepines	27.6	0.0	32.52	<.0001
(%) Other Opiates	25.3	0.0	29.46	<.0001

(%) Stimulants	19.5	0.0	22.10	<.0001
(%) Prescribed Benzodiazepines	13.8	0.0	15.17	<.0001
(%) Prescribed SSRIs	32.2	25.2	1.12	.29

3.1.3 Infant Characteristics

As shown in Table 5, there was a tendency for MM mothers to deliver earlier than comparison mothers but this difference did not reach statistical significance ($p = .09$). They did, however, deliver infants with significantly lower birth weights ($p < .0001$), smaller head circumferences ($p < .0001$) and were shorter in length ($p < .0001$) than comparison infants. Also as expected, 87.4% of ME children received treatment for NAS and no comparison children received treatment for NAS ($p < .0001$).

Table 5

Characteristics of ME and Comparison Infants at Term

Infant Clinical Data at Term	ME ($n = 87$)	Comparison ($n = 103$)	$t/\chi 2$	p
(%) NAS Treatment	87.4	0.0	149.96	<.0001
M (SD) Gestational Age (weeks)	38.79 (1.71)	39.21 (1.72)	-1.71	.09
M (SD) Birth Weight (*g*)	3058.41 (472.49)	3412.85 (586.74)	-4.53	<.0001
M(SD) Head Circumference (*cm*)	33.84 (1.53)	34.67 (1.47)	-3.80	<.0001
M (SD) Birth Length (*cm*)	50.16 (3.1)	52.16 (3.03)	-4.44	<.0001

3.2 Parent-Reported Child Behavioural and Emotional Adjustment at Age 4.5 Years

Table 6 describes the behavioural and emotional adjustment of the two study groups based on parent ratings on the SDQ at age 4.5 years. Significant differences were found across all scale scores, with parents of ME children being significantly more likely to report higher levels of child conduct, hyperactivity/inattention, emotional, peer and prosocial behaviour difficulties than parents of comparison children. The highest mean difference was reported on the hyperactivity/inattention scale of the SDQ, with a mean difference of 1.86 ($p < .0001$). The mean difference for conduct problems between the ME and comparison children was also high (mean difference= 1.55; $p < .0001$). Methadone-exposed children also had significantly more peer problems than comparison children, with a mean difference of 0.65 ($p = .002$). Methadone-exposed children and comparison children had a similar mean difference in emotional difficulties (mean difference= 0.64; $p = .01$). In terms of prosocial behaviour, ME children obtained a significantly lower prosocial score than comparison children (mean difference= -0.91; $p < .0001$). A large mean difference of 4.70 ($p < .0001$) for the total difficulties score was observed for ME and comparison children. Not surprisingly given the above findings, parents of ME children reported higher levels of distress and impairment associated with their child's difficulties as indicated by their higher impact scores, relative to parents of comparison children (mean difference= 0.60; $p = .001$).

Table 6

Parent-Reported Behavioural and Emotional Functioning of ME and Comparison Children at Age 4.5 Years

SDQ Scores	ME (n = 87) M(SD)	Comparison (n = 103) M(SD)	t	Mean difference (95% CI)	p
Conduct Problems Score	2.47 (1.90)	0.92 (1.11)	6.69	1.55 (1.09 - 2.01)	<.0001

Hyperactivity/ Inattention Score	4.28 (2.37)	2.42 (2.13)	5.70	1.86 (1.22 - 2.50)	<.0001
Emotional Symptoms Score	1.91 (1.88)	1.27 (1.42)	2.65	0.64 (0.16 - 1.11)	.01
Peer Problems Score	1.59 (1.56)	0.93 (1.22)	3.18	0.65 (0.25 - 1.06)	.002
Prosocial Score	7.80 (1.76)	8.72 (1.28)	-4.03	-0.91 (-1.36 - -0.47)	<.0001
Total Difficulties Score	10.24 (5.49)	5.54 (4.14)	6.56	4.70 (3.28 - 6.11)	<.0001
Impact Score	0.63 (1.66)	0.03 (0.17)	3.38	0.60 (0.25 - 0.96)	.001

Extending on the above analysis, we then examined the extent to which ME children had emotional and behavioural problems in the clinical range on the SDQ. These results are shown in Table 7, which reports the proportion of children whose scores placed them in the clinically at-risk range. As described in the Method, children were classified as falling within the clinical range if their scores exceeded the tenth percentile score of children in the comparison group (See page 52). That is, the abnormal range was specified according to the cut-point which separated the comparison children with scores in the most severe 10%.

All subscale scores excluding the emotional symptoms score (p = .05) resulted in statistically significant differences between the rates of clinical-range scores for ME and comparison children at age 4.5 years. The largest difference was between the ME and comparison children on the conduct problems subscale, with 42.5% ME and 10.7% comparison children falling within the abnormal range. Methadone-exposed children had 6.2 times the odds of scoring within this range (p < .0001). The hyperactivity/inattention subscale also resulted in clear between-group differences (p = .003), as ME children (27.6%) had 3.2 times the odds to have scores that fell within the abnormal range than comparison children (10.7%). Methadone-

exposed children (23%) had 2.5 times the odds of having scores within the abnormal range for peer problems than comparison children (10.7%) (p = .02). The prosocial subscale also resulted in statistically significant differences between ME (21.8%) and comparison (6.8%) children (OR= 3.83; p = .003). Although there were observed differences between ME and comparison children in emotional symptoms, this different was not statistically significant (p = .05). Finally, ME children had 4.5 times the odds of comparison children to have a total difficulties score within the clinical range (41.4% vs. 13.6%; $p < .0001$).

Table 7

SDQ Clinical Range Cut-off Scores for ME and Comparison Children at Age 4.5 Years

No. of Children in SDQ Clinical Range	ME (n = 87) (%)	Comparison (n = 103) (%)	$\chi 2$	Odds Ratio (95% CI)	p
Conduct Problems	42.5	10.7	25.34	6.19 (2.91- 13.18)	<.0001
Hyperactivity/Inattention Problems	27.6	10.7	8.97	3.19 (1.46- 6.97)	.003
Emotional Problems	18.4	8.7	3.85	2.35 (.98- 5.63)	.05
Peer Problems	23.0	10.7	5.23	2.50 (1.12- 5.56)	.02
Prosocial Behaviour	21.8	6.8	9.04	3.83 (1.53- 9.62)	.003
Total Difficulties	41.4	13.6	18.78	4.49 (2.21- 9.1)	<.0001

3.3 Risks of Early-Onset Psychiatric Disorders

Across each disorder category (i.e. externalising, internalising, and other disorders) rates of individual disorders were computed and then the overall "any" category rates were computed. Within the externalising disorder category, ADHD subtypes (ADHD Inattentive

type, ADHD Hyperactive-Impulsive type, ADHD Combined type) and Conduct/Oppositional Disorders (CD and ODD) were included. Rates of all ADHD subtypes were summed to create an "Any ADHD" category. Rates of both CD and ODD were combined to create an "Any Conduct/Oppositional" category. Within the Internalising/Other Disorder category, individual anxiety disorder and individual depressive disorder rates were computed, as well as the overall "any anxiety disorder" and "any emotional disorder" rates. Additionally, the rate of any disorder diagnosis was computed. Odds ratios (OR) with confidence intervals (CI) are reported for each of the composite variable "any" disorder diagnoses to provide a measure of effect size. The reporting of OR was confined to these summary measures since there were insufficient cases for the singular diagnosis variables to generate these.

3.3.1 Rates of Early-Onset Externalising Disorders

Table 8 reports the rates of externalising behaviour disorders in ME and comparison children at age 4.5 years. With respect to Attention Deficit Hyperactivity Disorder, ME children were subject to significantly higher rates of ADHD Combined (9.2% vs. 1.9%; p = .026) and any diagnosis of ADHD (14.9% vs. 1.9%; p = .001). Methadone-exposed children had almost nine times the odds of being diagnosed with any ADHD compared to comparison children. However, there were no significant differences between both groups of children on rates of ADHD Inattentive type (p = .12) and ADHD Hyperactive-Impulsive type (p = .06).

Similarly, between group differences were also observed for rates of Conduct and Oppositional disorders. Children in the ME group were subject to significantly higher rates of CD diagnoses (8% vs. 0%; p = .003), ODD diagnoses (14.9% vs. 1%; p < .0001), and any Conduct/Oppositional Diagnosis (19.5% vs. 1%; p < .0001). Methadone-exposed children had almost 25 times the odds of comparison children of receiving a diagnosis of Conduct/Oppositional Disorder. An "any externalising disorder" composite variable was created which comprised ADHD Combined, ADHD Inattentive, ADHD Hyperactive-

Impulsive, ODD and CD. Approximately 24% of ME children were diagnosed with an externalising disorder compared to 1.9% of non-exposed comparison children ($p < .0001$). Furthermore, the odds of ME children in being diagnosed with any externalising disorder were approximately 16 times that of the comparison group of children.

Table 8

Rates of DSM-IV Externalising Diagnoses as Assessed by the DAWBA for ME and Comparison Children at Age 4.5 Years

DAWBA Externalising Diagnoses	ME (n = 87) (%)	Comparison (n = 103) (%)	$\chi 2$	Odds Ratio (95% CI)	p
Attention Deficit Hyperactivity Disorder					
Inattentive	2.3	0.0	2.39	-	.12
Hyperactive-Impulsive	3.4	0.0	3.61	-	.06
Combined	9.2	1.9	4.98	-	.03
Any ADHD	14.9	1.9	10.96	8.87 (1.94- 40.51)	<.0001
Conduct/Oppositional Disorders					
Conduct Disorder	8.0	0.0	8.60	-	.003
Oppositional Defiant Disorder	14.9	1.0	13.49	-	<.0001
Any Conduct/Oppositional	19.5	1.0	18.96	24.77 (3.22- 190.43)	<.0001
Any Externalising Disorder	24.1	1.9	21.84	16.07 (3.65-70.81)	<.0001

3.3.2 Rates of Early-Onset Internalising Disorders and ASD

Table 9 presents the rates of emotional and other disorder diagnoses for ME and comparison children at age 4.5 years. As shown, the only other disorder to differentiate the two

groups was Separation Anxiety Disorder (SAD), which was significantly higher in the ME group compared to the comparison group (11.5% vs. 2.9%; $p = .02$). In contrast to the findings above on externalising disorders, whilst rates of emotional disorders were somewhat elevated in the ME group, no other conditions met the statistical significance threshold. Finally, no children in either group were diagnosed with Pervasive Developmental Delay/Autism.

Taken together, the results presented in Table 9 suggest ME children at age 4.5 are not at an increased risk of an internalising disorder diagnosis or an "other" disorder diagnosis, such as Pervasive Developmental Delay/Autism. Finally, the rates of a diagnosis of any psychiatric disorder for ME and comparison children was investigated. Methadone-exposed children had 4.4 times the odds of being diagnosed with any disorder compared to comparison children ($p < .0001$), which suggests that ME children are at an increased risk of being diagnosed with a psychiatric disorder in general.

Table 9

Rates of DSM-IV Internalising and Other Disorder Diagnoses as Assessed by the DAWBA for ME and Comparison Children at Age 4.5 Years

DAWBA Internalising and Other Diagnoses	ME ($n = 87$) (%)	Comparison ($n = 103$) (%)	$\chi 2$	Odds Ratio (95% CI)	p
Anxiety Disorders					
Separation Anxiety	11.5	2.9	5.45	-	.02
Specific Phobia	6.9	1.9	2.87	-	.09
Social Phobia	1.1	1.9	0.19	-	.66
Generalised Anxiety	1.1	2.9	0.71	-	.40
Any Anxiety Disorder	14.9	8.7	1.77	1.84 (0.74- 4.53)	.18
Depressive Disorders					

Major Depression	1.1	0.0	1.19	-	.28
Any Internalising Disorder	14.9	8.7	1.77	1.84 (0.74- 4.53)	.18
Other Disorders					
PDD/Autism	0.0	0.0	-	-	-
Any Disorder	34.5	10.7	15.79	4.40 (2.05- 9.47)	<.0001

3.4 Rates and Patterns of Comorbid Mental Health Disorders

Table 10 shows the proportion of children in each group who were subject to no, one, two or three disorder diagnoses. For this analysis, children meeting the criteria of any of the major disorder categories (i.e., Any ADHD) were coded as subject to problems in that disorder domain. Diagnoses included in this table include CD, ODD, any ADHD and any internalising disorder. As shown, ME children were more likely to be diagnosed with multiple co-occurring disorders compared to non-exposed comparison children ($p < .0001$). For both the ME and comparison group, a majority of children did not meet DSM-IV criteria for CD, ODD, ADHD, or an emotional disorder (65.5% & 89.3%, respectively). However, 18.4% of ME children had one diagnosis of any of these disorders and 9.7% of comparison children had one diagnosis. Only one child in the comparison group met criteria for two comorbid disorders. Approximately 14% of ME children had two of these diagnoses, and 2.3% ME children met criteria for three. Given the elevated rates of comorbid mental health disorders in the ME group of children, the nature of these comorbidities was further examined. This analysis was confined to children in the ME group with one or more disorder.

Table 10

Frequencies of Comorbid DAWBA Diagnoses in ME and Comparison Children at Age 4.5 Years

No. of Diagnoses	ME (n = 87) (N)	(%)	Comparison (n =103) (N)	(%)
0	57	65.5	92	89.3
1	16	18.4	10	9.7
2	12	13.8	1	1.0
3	2	2.3	0	0.0

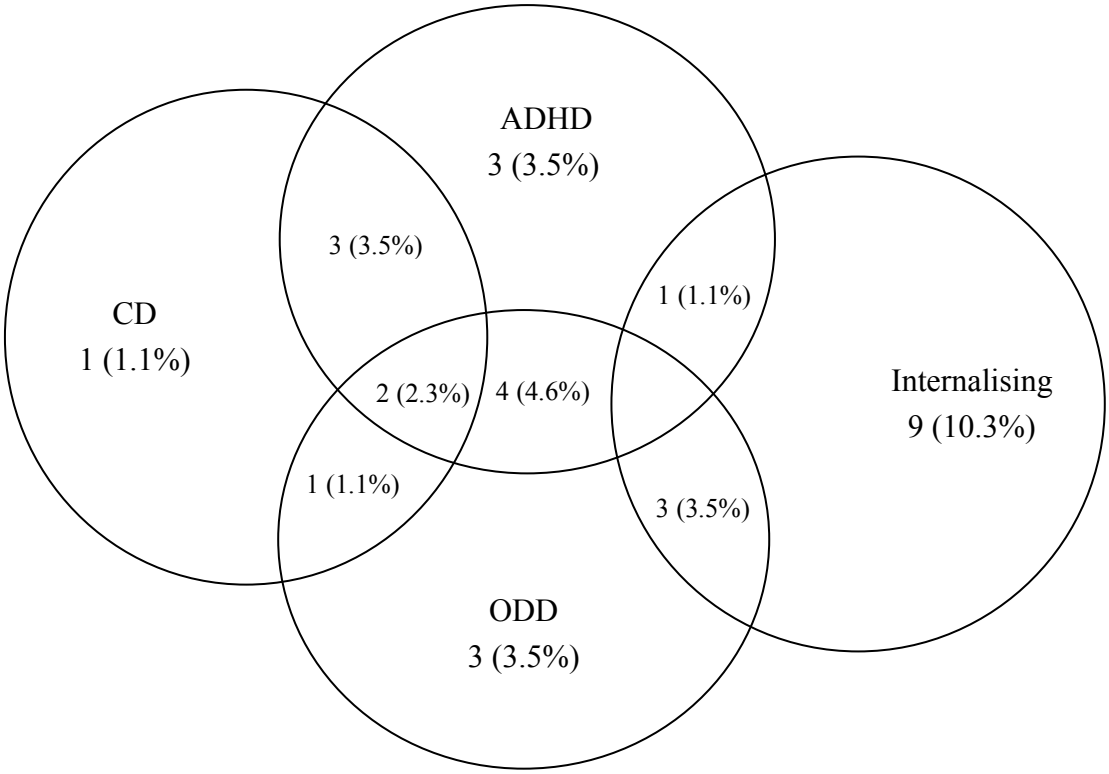
Note: $\chi 2 = 19.61$ (3); $p < .0001$.

Given the elevated rates of comorbid mental health disorders in the ME group, Figure 3 shows the pattern of co-occurring psychiatric disorders in ME children at age 4.5. Frequencies represent the children who were diagnosed with at least one disorder. Disorders included in this analysis included Conduct Disorder, Oppositional Defiant Disorder, ADHD (any) and any internalising disorder.

ADHD and ODD had the highest comorbidity rate, with four ME children meeting criteria for both disorders at 4.5 years (4.6%). More ME children had comorbid ADHD and ODD than ADHD or ODD alone (3.5% & 3.5%, respectively). ADHD and any internalising disorder had a comorbidity rate of 1.1%, with only one child meeting criteria for both of these disorders. Three ME children met criteria for both ADHD and CD (3.5%). Three children also met criteria for ODD and an internalising disorder (3.5%). One child met criteria for CD and ODD (1.1%). Lastly, two children met criteria for ADHD, CD, and ODD (2.3%). These results reflect the variability of diagnostic comorbidity patterns for preschool children prenatally exposed to methadone.

Figure 3

Patterns of DAWBA Comorbid Psychiatric Diagnoses in ME Children at Age 4.5 Years



3.5 Associations Between Prenatal Methadone Exposure and Mental Health Outcome After Covariate Adjustment

The above results suggest that ME children were at an increased risk of behavioural and emotional maladjustment on parent-report measures, as well as an elevated risk of meeting diagnostic criteria for externalising disorders at 4.5 years old, compared to comparison children. In contrast, ME children were not at an increased risk of meeting diagnostic criteria for internalising disorders at 4.5 years.

However, a further important question that needs to be addressed is the extent to which these elevated rates of mental health disorders reflect the direct effects of methadone, or might partially or fully reflect the effects of confounding variables correlated with maternal opioid

dependence and need for MMT. The following subsection explores the influence of confounding factors that could contribute to the higher rates of externalising behaviour disorder found in ME children at age 4.5 years. Internalising disorder diagnoses were not included in this analysis because of the low rates of these diagnoses and because no major significant differences were found. A binary logistic regression was conducted in order to determine the independent contributions of group status (ME or comparison), sex, birth weight, social risk, maternal nutrition, maternal mental illness during pregnancy, and poly-substance use to externalising behaviour diagnoses at 4.5 years old. These variables were all included in the analysis due to significant correlations with methadone maintenance group status in the present study and previous research. Within the covariate adjustment analysis, B refers to the values predicting the dependent variable from the independent variable and SE refers to the standard error of the coefficients. The purpose of this analysis was to investigate whether the relationship between group status and the externalising disorder outcome variables remained significant after including multiple infant and maternal psychosocial variables. Each of the major disorder outcomes that were found to be significant in the above bivariate analyses were examined individually and results were as follows.

Table 11 presents the results from the logistic regression analysis of the any ADHD outcome variable, which resulted in social risk being the only significant covariate of any ADHD diagnosis at age 4.5 years in the second model ($p = .03$). In the third model for Table 11, social risk remained the only variable significantly associated with ADHD ($p = .03$). Model 4 introduced maternal mental illness and poly-substance use during pregnancy into the model, which did not result in any significant covariates for any ADHD diagnosis. Social risk approached significance ($p = .07$), but was no longer significantly associated with ADHD at age 4.5. Group status was not significantly associated with ADHD in preschool aged children after controlling for various confounders.

Table 11

Hierarchical Logistic Regression Analysis of Covariates Associated with Any ADHD in ME Children at Age 4.5 Years

Variables Associated with ADHD	B (SE)	Odds Ratio (95% CI)	*p*
Model 1			
Group Status	-2.19 (0.78)	0.11 (0.03-0.51)	.01
Model 2			
Group Status	-1.01 (0.84)	0.37 (0.07-1.91)	.23
Child Sex	-1.09 (0.64)	0.34 (0.10-1.18)	.09
Birth Weight	-0.00 (0.00)	1.00 (1.00-1.00)	.12
Social Risk	0.61 (0.28)	1.83 (1.06-3.16)	.03
Model 3			
Group Status	-0.93 (0.97)	0.39 (0.06-2.61)	.33
Child Sex	-1.08 (0.64)	0.34 (0.10-1.19)	.09
Birth Weight	-0.00 (0.00)	1.00 (1.00-1.00)	.12
Social Risk	0.60 (0.28)	1.83 (1.06-3.16)	.03
Maternal Nutrition	-0.00 (0.01)	0.10 (0.97-1.03)	.87
Model 4			
Group Status	-0.47 (1.03)	0.63 (0.08-4.69)	.65
Child Sex	-1.14 (0.65)	0.32 (0.09-1.14)	.08
Birth Weight	-0.00 (0.00)	1.00 (1.00-1.00)	.29
Social Risk	0.54 (0.30)	1.72 (0.96-3.09)	.07
Maternal Nutrition	-0.00 (0.02)	1.00 (0.97-1.03)	.95
Maternal Mental Illness	1.09 (0.67)	2.97 (0.80-11.01)	.10
Poly-Substance Use	0.10 (0.15)	1.11 (0.83-1.47)	.49

Note: Outcome variable; No= 0, Yes= 1.

Table 12 presents the logistic regression results for any diagnosis of Conduct Disorder and/or Oppositional Defiant Disorder at age 4.5 years. Model 2 for Table 12 resulted in group status being significantly associated with any CD/ODD (p = .04). Social risk approached significance (p = .05). After introducing maternal nutrition in Model 3, group status remained significantly associated with any CD/ODD (p = .02). In the final model for Table 12, which included maternal mental illness and poly-substance use, group status remained significantly associated with CD/ODD (p = .02). Again, social risk approached significance but was not significantly associated with a diagnosis of CD/ODD at age 4.5 years (p = .05). This suggests that after controlling for various confounding factors, methadone exposure in-utero is the only significant predictor of a diagnosis of CD/ODD in preschool aged children, independent of confounding prenatal risk factors.

Table 12

Hierarchical Logistic Regression Analysis of Covariates Associated with Any CD/ODD in ME Children at Age 4.5 Years

Variables Associated with CD/ODD	B (SE)	Odds Ratio (95% CI)	*p*
Model 1			
Group Status	-3.14 (1.04)	0.04 (0.01-0.33)	.00
Model 2			
Group Status	-2.28 (1.11)	0.10 (0.01-0.90)	.04
Child Sex	-0.83 (0.59)	0.44 (0.14-1.39)	.16
Birth Weight	0.00 (0.00)	1.00 (1.00-1.00)	.48
Social Risk	0.45 (0.28)	1.56 (0.90-2.70)	.11
Model 3			
Group Status	-2.75 (1.19)	0.06 (0.01-0.66)	.02

Child Sex	-0.89 (0.60)	0.41 (0.13-1.33)	.14
Birth Weight	0.00 (0.00)	1.00 (1.00-1.00)	.50
Social Risk	0.49 (0.28)	1.63 (0.95-2.80)	.08
Maternal Nutrition	0.01 (0.01)	1.01 (0.99-1.04)	.27
Model 4			
Group Status	-2.94 (1.24)	0.05 (0.01-0.60)	.02
Child Sex	-0.89 (0.60)	0.41 (0.13-1.35)	.14
Birth Weight	0.00 (0.00)	1.00 (1.00-1.00)	.59
Social Risk	0.58 (0.30)	1.78 (1.00-3.18)	.05
Maternal Nutrition	0.01 (0.01)	1.01 (0.99-1.04)	.35
Maternal Mental Illness	0.49 (0.60)	1.63 (0.50-5.31)	.41
Poly-Substance Use	-0.17 (0.16)	0.84 (0.61-1.16)	.29

Note: Outcome variable; 0= No, 1= Yes

The rates of a diagnosis of any externalising disorder at age 4.5 years are presented in Table 13. Group status remained a significant predictor of any externalising disorder diagnoses for the first three models, but was no longer significant when maternal psychopathology during pregnancy and poly-drug use were included in the model ($p = .07$). After including all potential covariates in the equation, no variable remained a significant predictor of an externalising disorder diagnosis in children age 4.5 years old.

Table 13

Hierarchical Logistic Regression Analysis of Covariates Associated with Any Externalising Disorder in ME Children at Age 4.5 Years

Variables Associated with Externalising Diagnoses	B (SE)	Odds Ratio (95% CI)	*p*
Model 1			
Group Status	-2.72 (0.76)	0.07 (0.02-0.29)	.00
Model 2			
Group Status	-1.80 (0.82)	0.17 (0.03-0.83)	.03
Child Sex	-0.77 (0.52)	0.47 (0.17-1.30)	.14
Birth Weight	-0.00 (0.00)	1.00 (1.00-1.00)	.31
Social Risk	0.49 (0.24)	1.62 (1.01-2.61)	.05
Model 3			
Group Status	-2.06 (0.91)	0.13 (0.02-0.77)	.02
Child Sex	-0.80 (0.53)	0.45 (0.16-1.27)	.13
Birth Weight	-0.00 (0.00)	1.00 (1.00-1.00)	.31
Social Risk	0.50 (0.24)	1.65 (1.03-2.64)	.04
Maternal Nutrition	0.01 (0.01)	1.01 (0.99-1.03)	.50
Model 4			
Group Status	-1.76 (0.96)	0.17 (0.03-1.12)	.07
Child Sex	-0.85 (0.53)	0.42 (0.15-1.22)	.11
Birth Weight	0.00 (0.00)	1.00 (1.00-1.00)	.54
Social Risk	0.47 (0.25)	1.61 (0.98-2.64)	.06
Maternal Nutrition	0.01 (0.01)	1.01 (0.99-1.03)	.51
Maternal Mental Illness	0.80 (0.55)	2.22 (0.76-6.49)	.15
Poly-Substance Use	0.04 (0.13)	1.04 (0.81-1.34)	.76

Note: Outcome variable; 0=No, 1=Yes

4. DISCUSSION

Children born to opioid-dependent mothers treated with methadone during pregnancy are widely recognised to be an especially vulnerable group, given their likely exposure to a wide range of risk factors that can contribute to adverse developmental outcomes. Previous studies have identified heightened levels of behavioural issues in methadone-exposed children compared to non-exposed comparison children, such as aggression, hyperactivity, inattentiveness and lack of prosocial behaviour. However, findings on internalising difficulties in ME children are limited. This prospective, longitudinal study extended on existing research by examining the extent to which ME children were at risk of early-onset externalising and internalising problems and disorders at age 4.5 years old, compared to comparison children of the same age. Specifically, this study compared children's behavioural and emotional adjustment on the SDQ and risk of psychiatric disorder assessed using the DAWBA, which is a psychometrically valid diagnostic interview completed with a child's primary caregiver. Studies in this area to date have typically relied on parent-report screening measures and few have considered the influence of potential confounding factors such as social risk and maternal poly-drug use during pregnancy. They have also tended to have high sample attrition and poor measurement of maternal drug use during pregnancy. This study addressed these methodological issues and utilised an objective measure of psychiatric diagnoses in both ME and comparison children at age 4.5 years old as well as the caregiver-reported SDQ.

As hypothesised, the findings from this study showed that children born to mothers maintained on methadone during pregnancy had heightened levels of behavioural and emotional adjustment difficulties and were more at risk of meeting DSM-IV diagnostic criteria for a psychiatric disorder. Specifically, ME children were significantly more likely to meet criteria for an externalising behaviour disorder such as Attention-Deficit Hyperactivity

Disorder, Oppositional Defiant Disorder and Conduct Disorder. However, there were no significant between-group differences in internalising disorder risk. Additionally, ME children were significantly more likely to be diagnosed with comorbid externalising and internalising disorders. Even after taking into account other social risk and pregnancy factors, methadone exposure during pregnancy placed children at an increased risk of a diagnosis of ODD/CD. Major findings are discussed below in relation to each of the study aims.

4.1 Behavioural and Emotional Adjustment

The first aim of this thesis was to investigate the behavioural and emotional adjustment of ME and comparison children on the parent-reported Strengths and Difficulties Questionnaire. This screening measure includes five subscales measuring conduct problems, hyperactivity/inattention, emotional symptoms, peer problems and prosocial behaviour, and provides a total difficulties score and an additional impact supplement which evaluates the distress and impairment associated with the child's difficulties (Goodman & Scott, 1999). Scores on all subscales resulted in statistically significant differences between ME and comparison children. The conduct and hyperactivity/inattention subscales resulted in the largest mean differences. These findings support the first hypothesis made; mothers maintained on methadone during pregnancy reported heightened levels of behavioural adjustment difficulties such as conduct problems and hyperactivity/inattention in their preschool-aged children. This is consistent with other studies which have also reported increased levels of conduct problems and hyperactivity/inattention in opioid-exposed children (de Cubas & Field, 1993; Sandtorv et al., 2018; Sundelin-Wahlsten & Sarman, 2013). As hypothesised, ME children were also found to have significantly higher levels of emotional symptoms than non-exposed children. Compared to behavioural difficulties, emotional difficulties in ME preschool children are relatively understudied. de Cubas & Field (1993) and van Baar et al. (1994)

reported higher levels of depressive symptoms in opioid-exposed children. de Cubas and Field (1993) also reported heightened levels of anxiety in ME children. Lastly, ME children had significantly higher levels of peer problems and scored significantly lower than comparison children in prosocial behaviour. This suggests that ME children may experience increased difficulty with their social skills. Other studies have also reported significant difficulties with social adjustment in opioid-exposed children (de Cubas & Field, 1993; Hunt et al., 2008; Soepatmi, 1994; van Baar et al., 1994). The results from the current study in addition to previous research highlight the adjustment difficulties in multiple domains ME children may be subject to.

The findings from the administration of the SDQ mirror other studies that have utilised parent-report measures to assess behavioural and emotional adjustment. Previous studies have reported that methadone-exposed children to have significantly higher scores on the parent-report Child Behavior Checklist (CBCL) compared to non-exposed children (de Cubas & Field, 1993; Nygaard et al., 2016; Soepatmi, 1994), which also measures caregiver-reported behavioural and emotional difficulties in children. For example, Ornoy et al. (2001) found that children born to mothers addicted to heroin during pregnancy had the highest externalising behaviour scores on the CBCL compared to control children. However, other studies have found conflicting results. For example, Sundelin-Wahlsten and Sarman (2013) administered the SDQ to parents of buprenorphine-exposed children and found no significant problems on any of the five scales. Although, this study did not include a matched control group and the children were exposed to buprenorphine, not methadone. Speculatively, buprenorphine exposure in-utero may not have the same effect on long-term behavioural and emotional development in comparison to methadone and other opioids.

Further examination of the extent to which children's scores were in the high-risk range showed that approximately 43% of ME children fell within the clinical cut-off range for

conduct problems compared to 10.7% of comparison children (OR = 6.2). Relatedly, ME children also had approximately 3 times the odds of comparison children to obtain hyperactivity/inattention scores within the clinical cut-off range, with just over a quarter of ME children scoring above the 90th percentile. Methadone-exposed children were not significantly more likely to obtain emotional symptom scores within the clinical cut-off range. Multiple studies examined the rates of clinically significant hyperactivity, inattention and impulsivity in opioid-exposed children using parent-report measures. Ornoy et al. (2001) reported a significantly higher proportion of school-age heroin-exposed children having clinically significant inattention, hyperactivity and impulsivity compared to controls, with 54% of children born to heroin-dependent mothers raised at home obtaining scores above the clinical cut-off point on the Conners questionnaire. Approximately one quarter of adopted heroin-exposed children and children born to heroin-dependent fathers obtained clinically significant scores. Similarly, as reported by Nygaard et al. (2016), one-quarter of opiate-exposed children had clinically significant caregiver-reported ADHD-related symptoms on the ADHD Rating Scale, compared to no comparison children. These findings by Nygaard et al. are similar to the present study, as approximately one-quarter of opioid-exposed children had clinically significant hyperactivity, inattention and impulsivity in both studies. However, in the present study, no further analyses were done that explored the contribution of potential confounders. Due to this, it cannot be determined whether the results are solely due to methadone exposure during pregnancy or if birth, maternal and/or socio-familial factors also contribute to the children's scores.

4.2 DAWBA Externalising and Internalising Disorder Diagnoses

The current study also sought to investigate the risk of meeting diagnostic criteria for externalising and internalising disorders in ME and comparison children at age 4.5 years.

Further between-group differences in mental health disorder diagnoses were explored using the DAWBA, which provided computer-generated psychiatric diagnoses for the children. The results from the DAWBA were the primary focus of this thesis, as studies on psychiatric diagnoses of opioid-exposed preschool-aged children is a highly under-researched area. Consistent with results from the SDQ, ME children were significantly more likely to be diagnosed with an externalising behaviour disorder. However overall, relative to their same age non-exposed peers, ME children were not at an increased risk of developing an internalising disorder.

4.2.1 Conduct Disorder and Oppositional Defiant Disorder

Between-group differences in diagnoses of Conduct/Oppositional Defiant Disorder diagnoses were examined on the DAWBA. Children in the ME group were significantly more likely to meet criteria for a diagnosis of ODD, CD and CD/ODD. Approximately 15% of ME children were diagnosed with ODD, compared to 1% of comparison children. Conduct Disorder was less prevalent, with 8% of ME children diagnosed with CD, compared to no comparison children. Methadone-exposed children had almost 25 times the odds of being diagnosed with any CD and/or ODD compared to comparison children at age 4.5 years (19.5% vs. 1%).

The contributions of confounding factors to a diagnosis of CD/ODD at age 4.5 years were also investigated. After controlling for child sex, birth weight, social risk, maternal nutrition, maternal psychopathology and poly-substance use, group status remained the only significant predictor of CD/ODD (p = .02). This suggests that ME children are at an increased risk of developing CD or ODD at age 4.5 years old, even after taking into account other known maternal, clinical and social factors measured during the perinatal period that may play a role in the development of these disorders. This raises questions about the teratogenic mechanisms involved in the association between prenatal methadone exposure and early-onset CD/ODD.

Additionally, the potential impact of adverse postnatal experiences and trauma may also contribute to the rates of CD/ODD observed in ME children. Although the current study did not examine the impact of postnatal factors on psychiatric outcome, contextual family factors such as parenting practices, parental mental illness and marital conflict are associated with conduct and antisocial behaviour in children (Matthys & Lochman, 2017), with parenting behaviours functioning as a major key influence on child behaviour difficulties (Burke et al., 2002). Therefore, a potential avenue for future research could be to examine the postnatal factors that may increase the likelihood of ME children meeting diagnostic criteria for early-onset CD.

The significant association between prenatal methadone exposure and ODD/CD in the present study is consistent with an earlier study, which showed that opioid-exposed children in the first six years of life were significantly more likely to have a diagnosis of CD than non-exposed children (Azuine et al., 2019). Interestingly, opioid exposure was not as strongly associated with CD in children older than six years, which suggested a differential risk over the life course. This may also reflect changes in family circumstances over time as many of these children are often adopted or placed in care as they grow up.

Despite the low base rate of CD in preschool-age children, the prevalence of this disorder in this age range is concerning and emphasises the vulnerable nature of this population. Additionally, given the young age of the children studied, the present findings may not reflect the true rates of CD in ME children. Nock, Kazdin, Hiripi, and Kessler (2006) conducted a retrospective assessment of CD using DSM-IV criteria in a representative sample of US adults and reported a median age of onset of approximately 11 ½ years old. However, the age of onset ranged widely within individuals and the retrospective nature of the study may have resulted in participants forgetting events and/or the timing of them (Nock et al., 2006). Regardless, this suggests that symptoms of CD may be most commonly observed in the

childhood years. In this study, 8% of ME children were diagnosed with CD. As children get older and their environment grows in complexity, the prevalence of CD in ME children may increase or depending on their developmental trajectory, decrease. Additionally, since ODD often precedes CD, the high prevalence rate of early-onset ODD may subsequently lead to increased risk of later diagnoses of childhood-onset CD.

4.2.2 Attention-Deficit Hyperactivity Disorder

Methadone-exposed children had almost 9 times the odds of being diagnosed with any type of ADHD compared to comparison children. Specifically, ME children were significantly more likely to meet DSM-IV diagnostic criteria for ADHD Combined type (9.2% vs. 1.9%). However, there were no significant between-group differences in the rates of children meeting diagnostic criteria for ADHD Hyperactive-Impulsive type and ADHD Inattentive type.

The relationship between methadone exposure and an ADHD diagnosis at age 4.5 years was further examined by investigating the contributions of various confounding variables measured during the perinatal period. Results showed that after controlling for child sex, birth weight, social risk, maternal nutrition, maternal mental illness during pregnancy and poly-substance use during pregnancy, between-group differences in the risk of ADHD were reduced to non-significance ($p = .65$). These results suggest that ADHD does not reflect the teratogenic effects of methadone in-utero but rather likely reflects the effects of other adverse exposures correlated with maternal methadone treatment.

These results are somewhat similar to findings from a study by Ornoy et al. (2001), who found that children exposed to opioids prenatally who had been adopted and were no longer living with their biological mother had significantly lower rates of ADHD symptoms compared to opioid-exposed children who were still living with their biological mother. Findings from Ornoy et al. (2001) suggest that the environment the child is raised in is an important mediator between opioid exposure and behavioural outcome. In comparison to the

present study, the children participating in the study by Ornoy et al. were of school age, which may be why elevated levels of clinically significant hyperactivity, inattention and impulsivity were observed. According to DSM-5 diagnostic criteria for ADHD, several Hyperactive-Impulsive or Inattentive symptoms must occur in two or more settings (American Psychiatric Association, 2013). Therefore, once children reach school age, prevalence rates of ADHD in ME children may be increased as this is when attentional difficulties are most often detected, given that children are expected to sit at a desk for increased periods and pay attention during class. A child who is unable to sustain their attention and regulate their behaviour may struggle to complete their work, which may result in classroom disruption. This is further supported by the findings by Azuine et al. (2019), who found that opioid exposure was associated with an increased risk of ADHD in school-aged children compared to preschool-aged children. This may be why prenatal methadone exposure was not significantly associated with any diagnosis of ADHD at 4.5 years in the present study, as the presentation of ADHD may vary according to the child's stage of development. Therefore, further longitudinal follow-up of these children will be important.

4.2.3 Rates of Any Externalising Disorder

A composite variable consisting of ADHD, CD and ODD diagnoses was summed to create an "Any Externalising Disorder" variable. Approximately one-quarter of ME children were diagnosed with any externalising disorder, compared to only 1.9% of comparison children. However, after controlling for child sex, birth weight, social risk, maternal nutrition, maternal mental illness during pregnancy, and poly-substance use during pregnancy, significance attenuated and the difference was no longer statistically significant. This could be due to the influence of ADHD included in the composite variable. These results suggest that ME children are at a high risk of developing externalising disorders and that the developmental

mechanisms are complex, reflecting the effects of maternal poly-drug use and other adverse prenatal exposures.

4.2.4 Internalising and Other Disorders

This study also examined children's risks for a range of internalising disorders, including Anxiety and Depressive Disorders. There were no significant differences in any internalising disorder diagnoses except for rates of Separation Anxiety Disorder (SAD). Methadone-exposed children scored significantly higher for rates of SAD, however, no further analyses were made to explore the effects of potential confounding variables. Therefore, this finding should be interpreted with caution. Regardless, SAD in young children is developmentally normative so this may explain the elevated rates of this disorder. Given the high-risk familial circumstances, maternal mental health difficulties and parental changes children exposed to methadone in-utero are likely to experience, this may result in an increased risk of developing SAD. In the same cohort of children as the present study, Lean, Prichard and Woodward (2013) reported that 44% of children born to mothers maintained on methadone during pregnancy had been removed from the custody of their biological mother by the time they turned 4.5 years old. Speculatively, this early-onset environmental and familial instability may contribute to the elevated rates of SAD in ME children. The association between prenatal methadone exposure and SAD in young children and the contribution of environmental risk factors is a potential avenue for future research.

These findings from the DAWBA aligned with the results obtained from the SDQ screening measure clinical cut-off points. Thus, taken together, the findings from the SDQ and DAWBA suggest that ME children do not, at least at this early age, appear to be at an increased risk of developing an internalising disorder. However, some caution is needed in the interpretation of these results, given the young age of the children studied and the fact that internalising disorder rates were still elevated with approximately 15% of ME children

diagnosed with any internalising disorder compared to 8.7% of comparison children. It is therefore possible that with increasing age, ME children may still be at risk. Subclinical internalising difficulties may eventuate into clinical disorder later in childhood. Another possible explanation is that children may manifest emotional difficulties as externalising behaviour problems. Alternatively, sometimes internalising disorders can be missed in young children who may not be able to verbally express negative emotions they are experiencing.

The current study also assessed the rates of Autism Spectrum Disorder (ASD) in ME and comparison children, as it is a developmental disorder that often emerges early. However, no children from either group met diagnostic criteria for ASD. Since ASD has a low base rate in the general population, it is necessary to have a larger sample size. The present study would be too underpowered to adequately examine the rates of ASD in ME children. Future research, ideally involving a larger sample is potentially warranted as Sandtorv et al. (2018) reported increased symptoms associated with ASD in opioid-exposed children aged approximately ten years old.

4.2.5 Comorbid DAWBA Disorders

As expected, results revealed high rates of diagnostic comorbidity in ME compared to comparison children. Methadone-exposed children had significantly higher rates of comorbidity compared to comparison children. One comparison child met diagnostic criteria for two psychiatric disorders at age 4.5, whereas 14 ME children met criteria for two or more psychiatric disorders. Three children met criteria for a single diagnosis of ADHD, however, ten children met criteria for ADHD and either ODD, CD, or an emotional disorder. Similarly, only three children met criteria for a single diagnosis of ODD. In contrast, nine children met criteria for an emotional disorder and four children met criteria for an emotional disorder and either ODD or ADHD. The highest comorbidity rate was between ODD and ADHD, with four

children meeting criteria for both of these disorders. Although ODD often functions as a precursor for CD, children meeting criteria for both ODD and CD may suggest these children exhibited oppositionality as well as more severe conduct behaviours. Therefore, the presence of ODD and CD in ME preschool children can function as an indication of severity. To date, no other studies have explored co-occurring psychiatric disorders in ME preschool children. Therefore, although comorbid mental health disorders in ME children were not explored extensively, the findings of the current study suggest a need for further research surrounding this issue. Studies have noted high comorbidity rates, suggesting approximately 54 -84% of children and adolescents with a diagnosis of ADHD may also meet diagnostic criteria for ODD and are at risk of developing CD (Pliszka, 2007). In the present study, approximately 77% of ME children who met criteria for ADHD also met criteria for another mental health disorder. These results suggest that children exposed to methadone during pregnancy are at an increased risk of meeting diagnostic criteria for more than one mental health disorder compared to non-exposed peers, further highlighting the clinical complexity of these children.

4.2.6 Issues with Diagnosing Psychiatric Disorders in Preschool

Egger and Angold (2006) note several concerns associated with the identification and classification of different forms of psychopathology in preschool children. These concerns include the difficulty associated with accurately assessing symptoms due to the rapid development in multiple domains, lack of consideration of developmental variation in dominant classification systems, risk of labelling children with diagnoses that alter perceptions of the child, and individual differences in the child that may be mistakenly attributed to psychopathology (Egger & Angold, 2006). Additionally, some existing psychiatric measures may not be designed to appropriately distinguish between developmentally normative behaviour in preschool-aged children and psychopathology (Bufferd, Dougherty, Carlson, Rose, & Klein, 2012). Although both the SDQ and the DAWBA have been designed to

effectively assess externalising and internalising difficulties and disorders in children from preschool to adolescence, it should be acknowledged that the children in this study were at the lower end of the normative age range. Keenan and Wakschlag (2002) reviewed the evidence on the consideration of preschool behavioural problems within a diagnostic framework and concluded that typical and atypical behaviour problems can be distinguished in early childhood and the DSM can be applied effectively to identify impairing disruptive behaviours (Keenan & Wakschlag, 2002). However, more research is required to understand the clinical implications of early-onset diagnoses of childhood mental health disorders and effective treatments for these conditions.

4.3 Additional Issues and Implications of Findings

Although postnatal factors that might contribute to ME children's mental health difficulties at age 4.5 were not examined in this thesis, these factors likely also play an important role in placing ME children at increased mental health risk. For example, factors such as parenting behaviours, parental mental health difficulties, familial and environmental instability could influence children's mental health outcome. Given many of the mothers maintained on methadone during pregnancy have additional psychosocial challenges, the effects of postnatal trauma could be relevant to the ME population of children. These maternal psychosocial challenges may expose the child to more risk factors that can influence the likelihood of externalising and internalising disorders.

The significant mental health difficulties in a young population of children also raise concerns about the academic outcomes of ME children. Since the children had not yet reached school age, any potential academic difficulties were unknown in the present study. However, in a prospective longitudinal study on the same cohort of children at 9.5 years old, ME children were found to be at risk of having significant educational delays, performing below the average

expected levels of achievement (Lee, Woodward, & Henderson, 2019). However, the learning difficulties of opioid-exposed children remain relatively under-studied compared to other neurodevelopmental outcomes. Children prenatally exposed to methadone have been found to have significant behavioural issues which are likely to persist through to school age (given their high-risk contexts). Speculatively, disruptive behaviour which interferes with teaching and the child's learning may contribute to lower educational achievement. Therefore, specialised support could be beneficial for methadone-exposed children's behavioural and emotional adjustment during the transition into primary school to promote academic success and social adjustment.

Overall, these findings highlight the importance of timely early intervention for children born to mothers maintained on methadone to help treat externalising behaviour disorders and prevent the development of further internalising and externalising difficulties. The increased likelihood of methadone-exposed children to experience multiple mental health difficulties increases the risk of an even poorer long-term outcome. Therefore, it is of critical importance that these children receive early intervention. Early intervention approaches such as family-focused interventions can help reduce symptoms of mental health difficulties in young children and impairment associated with these difficulties (Gleason, Goldson, & Yogman, 2016). These findings also bring attention to the importance of psychosocial support for the mothers and families of children exposed to methadone in-utero. As discussed, mothers maintained on methadone are significantly more likely to experience high levels of social risk, poly-substance use and mental illness. Therefore, targeted social support should be given to mothers participating in methadone maintenance treatment to reduce the number of risk factors the children are exposed to. Since these maternal and social risk factors can accentuate the early-onset mental health risk of methadone-exposed children, increased psychosocial support

services for pregnant women maintained on methadone in combination with early intervention for children may help to avert these developmental risks.

4.4 Strengths and Limitations of the Current Study

4.4.1 Strengths

The present study sought to address many of the limitations of previous studies. First, as discussed in Chapter 1, a major issue that is often inherent to drug outcome studies are the high rates of attrition. In the current study, 81% of the identified ME children completed the 4.5-year assessment and 90% of the identified comparison children completed the 4.5-year assessment. Although participants were still lost at follow-up, retention rates remained high, helping to maximise the representativeness of the sample and generalisability of study findings to ME and non-exposed preschoolers in New Zealand.

Second, the present study utilised random maternal urine samples during pregnancy and analysis of infant meconium to assess maternal drug use. Maternal self-report of drug use during pregnancy was also assessed. This is a strength of the study as a vast amount of previous research measured maternal poly-drug use during pregnancy using only maternal self-report, which can be prone to under-reporting. As well as detecting the presence of substance use during pregnancy, toxicology analysis can also help determine the type of substances used.

Third, a significant strength of the current study included the objective measure of diagnosable disorders in ME children. To date, no other study on ME children has generated mental health diagnoses for preschoolers using a structured parent interview. Provisional diagnoses were accepted or rejected by a clinician, generating a definitive diagnosis. This clinician was also blind to the children's study group. The use of the SDQ in addition to the DAWBA is also a strength in the present study, providing a parent-report account of behavioural and emotional problems as well as an objective psychiatric measure.

Finally, the present study controlled for various confounding factors that may also contribute to externalising disorder diagnoses in preschool children. Many previous studies did not adequately control for confounding factors, therefore making it difficult to assess the independent effects of opioid-exposure on child outcomes. The present study controlled for poly-drug use, whereas no previous studies did. This is a significant strength since various substances have also been found to have neurodevelopmental effects in-utero, such as cannabis and alcohol (Williams & Ross, 2007).

4.4.2 Limitations

Like virtually all studies on children exposed to substances in-utero, this study is subject to methodological limitations. One limitation of this study was the use of parent-report measures (SDQ) to assess the children's behaviour problems. A major issue that can arise during the use of parent-report measures is parental response bias. Definitions of the behaviours assessed can be specific to that individual and differ between parents (Aspland & Gardner, 2003). Parent-report of child behaviour can be altered by systematic biases such as parental mood (Aspland & Gardner, 2003), which can influence perceptions of the child's behaviour. When mothers are experiencing feelings of depression, they can be more likely to perceive their children's behaviour as problematic (Panaccione & Wahler, 1986; Najman et al., 2000). Additionally, the use of parental self-report for child behavioural problems could result in under-reporting of behaviour. Parental report measures can be prone to desirability bias, which suggests that some parents could answer the questions in a way that portrays them or their children in a more socially acceptable or desirable way. However, parent reports of behaviour are also highly beneficial as parents can observe the child in many contexts and across various periods. As discussed in the method section of this thesis, the SDQ is a valid, reliable measure of child and youth behavioural and emotional adjustment. The additional use of an objective

clinical measure to measure mental health difficulties, such as the DAWBA in the present study, can mitigate the subjective nature of parent-report.

Another limitation is the potential for other confounding variables that may not have been controlled for during analysis. The current study did not control for factors that may be present in the child's postnatal environment. Adverse child, maternal and familial factors occurring between birth and the 4.5-year psychological assessment can be considered mediators of the relationship between prenatal methadone exposure and mental health outcome, which were not the focus of the present study. Confounding factors correlated with maternal methadone use that occurred within the pregnancy/birth period were the primary focus.

Lastly, this study is limited by the age group that was assessed. At age 4.5 years old, there is a low base rate of psychiatric disorders compared to older children. Further follow-up of these children is necessary to assess the trajectory and stability of disorders. As children grow older, their cognition and behaviour also grow in complexity (Nygaard et al., 2016). Therefore, future research on the mental health outcomes of ME children at older ages and across both home and school settings will be important for further understanding of the extent and nature of their mental health difficulties.

4.5 Future Research Directions

In the current study, mothers who were maintained on methadone during pregnancy were found to have markedly higher rates of adverse socio-familial factors that may expose children to high-risk contexts throughout childhood. Therefore, this raises further concern about the influence and contribution of these factors to the future developmental trajectory of these children. As discussed in the limitations, this study did not explore the potential mediating factors that may be present in the relationship between methadone exposure in-utero and child mental health outcome. Further research which explores postnatal mediating factors such as

parent-child interaction, trauma, stress and parenting may help to provide a clearer picture of methadone exposure effects. Additionally, it could be beneficial to investigate the protective factors that may attenuate the risk of mental health difficulties in ME children and promote resilience. Protective factors at the individual, familial and wider community level may be associated with a decreased risk of child psychiatric difficulties.

Future research could also explore teacher-reported externalising and internalising behaviour difficulties in ME children. The DAWBA often incorporates teacher-reported information about children's difficulties during the psychological assessment. This comprehensively gathers information on the child's behaviour at home and in the school setting (Goodman et al., 2000). The use of both caregiver and teacher report can provide information on the extent to which child behavioural and emotional difficulties are pervasive across different environmental conditions or whether observed difficulties may be situational or confined to a single setting, such as at home or school.

4.6 Conclusion

The present study aimed to investigate the extent of parent-reported behavioural and emotional maladjustment in ME and comparison preschool children. The rates of DSM-IV externalising and internalising disorders were also examined for both groups. Diagnostic comorbidities were also assessed in the ME group. The last aim of the present study was to investigate the potential confounding factors during pregnancy/birth that may also contribute to the observed outcomes. As hypothesised, ME children had elevated levels of conduct problems, hyperactivity/inattention, emotional symptoms and peer problems compared to comparison children, as measured on the SDQ. Methadone-exposed children also had lower levels of prosocial behaviour. Further analysis of the children who fell within the clinically significant range of the SDQ subscales revealed statistically significant differences between ME and comparison children on all subscales except for the emotional subscale, which

approached significance (p = .05). Methadone-exposed children were also more likely to be diagnosed with an externalising disorder, however, they were not at risk of meeting diagnostic criteria for an internalising disorder at 4.5 years old. Further exploration of confounding variables correlated with maternal methadone use during pregnancy resulted in attenuation of group status significance for ADHD but not for CD/ODD. In-utero methadone exposure was the only variable that significantly predicted CD/ODD at 4.5 years old, despite the presence of multiple birth/maternal risk factors. Methadone-exposed children were also significantly more likely to be diagnosed with co-occurring mental health disorders. However, further follow-up of the developmental trajectory of these disorders is needed.

The findings from the present study highlight the importance of ME children's prenatal environment and the effects of adverse maternal and social risk factors on long-term development. Not only are ME children at risk of behavioural and emotional maladjustment and developing mental health disorders during the preschool years, but their complex environment can exacerbate the risk. The combination of teratogenic exposure as well as adverse birth, maternal and social risk factors accentuates the vulnerability of ME children and their mothers. The high rates of psychiatric disorders at such an early age combined with high levels of comorbidity raise particular concerns for the welfare of these children. Early intervention and specialised long-term support for children, mothers and families involved with methadone maintenance treatment is necessary and will hopefully result in positive developmental outcomes for children.

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6. APPENDICES

APPENDIX A: THE STRENGTHS AND DIFFICULTIES QUESTIONNAIRE

Strengths and Difficulties Questionnaire **P 4-10**

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain. Please give your answers on the basis of your child's behaviour over the last six months.

Your child's name ..... Male/Female

Date of birth.....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children, for example toys, treats, pencils	☐	☐	☐
Often loses temper	☐	☐	☐
Rather solitary, prefers to play alone	☐	☐	☐
Generally well behaved, usually does what adults request	☐	☐	☐
Many worries or often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, depressed or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets along better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Good attention span, sees chores or homework through to the end	☐	☐	☐

Do you have any other comments or concerns?

Please turn over - there are a few more questions on the other side

Overall, do you think that your child has difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

No	Yes- minor difficulties	Yes- definite difficulties	Yes- severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress your child?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with your child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
HOME LIFE	☐	☐	☐	☐
FRIENDSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐
LEISURE ACTIVITIES	☐	☐	☐	☐

- Do the difficulties put a burden on you or the family as a whole?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Signature ..... Date .....

Mother/Father/Other (please specify:)

Thank you very much for your help

APPENDIX B: DAWBA INTERVIEW AT 4.5 YEAR ASSESSMENT

CANTERBURY CHILD DEVELOPMENT STUDY

MATERNAL INTERVIEW SUPPLEMENT

CHILD HEALTH AND WELLBEING

4.5-Years

CODE			
INTERVIEWER			
	DD	**MM**	**YY**
DATE			

CHILDS DEVELOPMENT AND WELL BEING

SDQ Scale Card

SDQ Emotion Score	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
SDQ Hyperactivity Score	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
SDQ Conduct Score	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
SDQ Peer Score	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
SDQ Prosocial Score	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Peer minus Prosocial

(positive score reflects peer score > prosocial score)

(negative score reflects peer score < prosocial score)

SAS score

SECTION 1.2 - Friendships

Fr 1 What is [Name] like at making friends?

Finds it harder than average	About average	Finds it easier than average
0	1	2

Fr 2 What is [Name] like at keeping the friends s/he has made?

Finds it harder than average	About average	Finds it easier than average
0	1	2

Fr 3 At present, how many friends does s/he have that s/he fairly often spends time with, for example chatting, or doing things together, or going out as part of a group?

None	One	2-4	5-9	10+
0	1	2	3	4

Next section Fr 4

SECTION 1.3 – Separation Anxiety (worries and concerns that children might have)

Most children are particularly attached to a few key adults, looking to them for security and comfort, and turning to them when upset or hurt.

		No or Not Applicable	Yes
1.3.1	Is [Name] specially attached to the following adults?		
a)	Mother (biological or adoptive)	0	1
b)	Father (biological or adoptive)	0	1
c)	Another mother figure (stepmother, foster mother, father's partner)	0	1
d)	Another father figure (stepfather, foster father, mother's partner)	0	1

1.3.1	Is [Name] specially attached to the following adults?	No or Not Applicable	Yes
e)	One or more grandparents	0	1
f)	One or more other adult relatives (e.g. aunt, uncle, grown-up brother or sister)	0	1
g)	Childminder, nanny, au pair	0	1
h)	One or more teachers	0	1
i)	One or more other adult non-relatives (e.g. a family friend or neighbour)	0	1
j)	[ ] Not specially attached to any adult	0	1

If 1.3.1j was ticked, ask 1.3.1k , 1.3.1l and 1.3.1m; otherwise continue with 1.3.2

	Is [(Child) specially attached to the following children or young people?	No or Not Applicable	Yes
k)	One or more brothers, sisters or other young relatives	0	1
l)	One or more friends	0	1
m)	[ ] Not specially attached to anyone	0	1

If 1.3.1m is ticked, then skip to section 2 (Fears of specific things or situations). Otherwise continue:

1.3.2 You've just told me who [Name] is specially attached to: *If you want, you can list all from 1.3.1 that were answered 'Yes'*: From now on I am going to refer to these people as his/her 'attachment figures'

What I'd like to know next is how much [Name] worries about being separated from his/her attachment figures. Most children have some worries of this sort, but I'd like to know how [Name] compares with other children of his/her age. I am interested in how s/he is usually- not on the occasional 'off day'.

Overall, in the **last 4 weeks**, has s/he been particularly worried about being separated from his/her attachment figures?	No	Yes
	0	1

If 1.3.2 = Yes or if SDQ emotion score is ≥3 then continue. If neither skip to section 2 (Fears of specific things or situations)

1.3.3 Over the last 4 weeks, and compared with other children of the same age……

		No more than others (or Not applicable)	A little more than others	A lot more than others
a)	has s/he worried either about something unpleasant happening to his/her attachment figures, or about losing them?	0	1	2
b)	has s/he worried unrealistically that s/he might be taken away from his/her attachment figures e.g. by being kidnapped, taken to hospital or killed?	0	1	2
c)	has s/he not wanted to go to school in case something nasty happened to his/her attachment figures while s/he was away at school? (*Do not include reluctance to go to school for other reasons e.g. fear of bullying or exams*)	0	1	2
d)	has s/he worried about sleeping alone?	0	1	2
e)	has s/he come out of his/her bedroom at night to check on, or to sleep near, his/her attachment figures?	0	1	2
f)	has s/he worried about sleeping in a strange place?	0	1	2
g)	*(Only ask if aged under 11)* has s/he been afraid of being alone in a room at home without his/her attachment figures even if they are close by?	0	1	2
h)	*(Only ask if aged under 11)* has s/he been afraid of being alone at home if his/her attachment figures pop out for a moment?	0	1	2
i)	has s/he repeated nightmares or bad dreams about being separated from his/her attachment figure?	0	1	2

		No more than others (or Not applicable)	A little more than others	A lot more than others
j)	has s/he had headaches, stomach aches or felt sick when s/he had to leave his/her attachment figures or when s/he knew it was about to happen?	0	1	2
k)	has being apart from his/her attachment figures, or the thought of being apart from them led to worry, crying, tantrums, clinginess or misery?	0	1	2

If any of the items in 1.3.3 have been answered "A lot more than others" then continue with 1.3.4. If not, skip to section 2 (Fears of specific things or situations)

		No	Yes
1.3.4	Have [Name's] worries about separation been there for at least **4 weeks?**	0	1

1.3.5	How old was s/he when his/her worries about separation began? (if since birth, enter 0)		years old

		Not at all	A little	A medium amount	A great deal
1.3.6	How much have these worries upset or distressed him/her?	0	1	2	3

		Not at all	A little	A medium amount	A great deal
1.3.7	Have these worries interfered with……				
a)	How well s/he gets on with you and the rest of the family?	0	1	2	3
b)	Making and keeping friends?	0	1	2	3
c)	learning or class work?	0	1	2	3
d)	playing, hobbies, sports or other leisure activities?	0	1	2	3

		Not at all	A little	A medium amount	A great deal
1.3.8	Have these worries put a burden on you or the family as a whole?				

0	1	2	3

SECTION 2 - Fears of specific things or situations

This section of the interview is about some things or situations that children are often scared of, even though they aren't really a danger to them. I'd like to know what [Name] is afraid of. I am interested in how s/he is usually – not on the occasional 'off day'. Not all fears are covered in this section – some are covered in other sections e.g. fears of social situations, dirt, separation, crowds.

2.1 Is [Name] scared of any of the things or situations on this list?

		No	A little	A lot
a)	Animals: Dogs, spiders, bees and wasps, mice and rats, snakes, or any other animal, bird or insect	0	1	2
b)	Some aspect of the natural environment, e.g. storms, thunder, heights, water	0	1	2
c)	The dark	0	1	2
d)	Loud noises, e.g. fire alarms, fireworks	0	1	2
e)	Blood – injection – injury: Set off by the sight of blood or injury, or by an injection, or by other medical procedures	0	1	2
f)	Dentists or doctors	0	1	2
g)	Vomiting, choking or getting particular diseases, e.g. cancer or AIDS	0	1	2
h)	Using particular types of transport, e.g. cars, buses, boats, planes, ordinary trains, underground trains, bridges	0	1	2
i)	Small enclosed spaces, e.g. lifts, tunnels	0	1	2
j)	Using the toilet, e.g. at school or in someone else's house	0	1	2
k)	Specific types of people, e.g. clowns, people with beards, with crash-helmets, in fancy dress, dressed as Santa Claus	0	1	2
l)	Imaginary or supernatural beings, e.g. monsters, ghosts, aliens, witches	0	1	2
m)	Any other specific fear (Describe)…… ..... ……..	0	1	2

If any of the items in 2.1 have been answered 'a lot' then continue with 2.2. Otherwise go to Section 3.

2.2 Are any of these fears a real nuisance to him/her, to you, or to anyone else?

No	Perhaps	Definitely
0	1	2

If 2.2 = "Definitely" or if SDQ emotion score is ≥3 then continue. If neither, then skip to Section 3.

2.3 How long has this fear or the most severe of these fears been present?

Less than 1 month	1-5 months	6 months or more
0	1	2

2.4 When [Name] comes up against the things s/he is afraid of, or when s/he thinks s/he is about to come up against them, does s/he become anxious or upset?

No	A little	A lot
0	1	2

2.7 2.5

2.5 Does s/he become anxious or upset every time, or almost every time, s/he comes up against the things s/he is afraid of?

No	Yes
0	1

2.6 How often do his/her fears result in his/her becoming upset like this?

N.B. If [Name] is afraid of something that is only there for part of the year (e.g. wasps), this question is about that particular season.

Every now and then	Most weeks	Most days	Many times a day
0	1	2	3

2.7 Do [Name's] fears lead to him/her avoiding the things s/he is afraid of?

No	A little	A lot
0	1	2

2.9 2.8

2.8 Does this avoidance interfere with his/her daily life?

No	A little	A lot

0	1	2

2.9 Do you think that his/her fears are over the top or unreasonable?

No	Perhaps	Definitely
0	1	2

2.10 And what about him/her? Does s/he think that his/her fears are over the top or unreasonable?

0	1	2

2.11 Have [Name's] fears put a burden on you or the family as a whole?

Not at all	A little	A medium amount	A great deal
0	1	2	3

SECTION 3 – Fear of social situations

I am interested in whether [Name] is particularly afraid of social situations. This is compared with other children of his/her age, and is not counting the occasional 'off day' or ordinary shyness.

3.1 Overall, does [Name's] particularly fear or avoid social situations that involve a lot of people, meeting new people, or doing things in front of people?

No	Yes
0	1

If 3.1 = "Yes" or if SDQ emotion score is ≥3, then continue. If neither, then skip to section 4.

3.2 Has [Name] been particularly afraid of any of the following social situations over the last 4 weeks?

	No	A little	A lot
a) Meeting new people?	0	1	2
b) Meeting a lot of people, such as at a party?	0	1	2
c) Eating in front of others?	0	1	2
d) Speaking in class?	0	1	2
e) Reading out loud in front of others?	0	1	2
f) Writing in front of others?	0	1	2

If none of the items in 3.2 have been answered "A lot", skip to section 4; otherwise continue.

3.3 Most children are attached to a few key adults, feeling more secure when they are around. Some children are only afraid of social situations if they don't have one of these key adults around.

Other children are afraid of social situations even when they are with one of these key adults.

Which is true for [Name]?	Mostly fine in social situations as long as key adults are around	Social fears are marked even when key adults are around
	0	1

3.4 Is [Name] just afraid with adults, or is s/he also afraid in situations that involve a lot of children, or meeting new children?

Just with adults	Just with children	With both adults and children
0	1	2

3.5 Outside of these social situations is {name} able to get on well enough with the adults and children s/he knows best?

No	Yes
0	1

3.6 Do you think his/her dislike of social situations is because s/he is afraid s/he will act in a way that will be embarrassing or show him/her up?

No	Perhaps	Definitely
0	1	2

(Only ask if 3.2d='A lot' or 3.2e = 'A lot' or 3.2f = 'A lot')

3.7 Is his/her dislike of social situations related to specific problems with speech, reading or writing?

No	Perhaps	Definitely
0	1	2

3.8 How long has his/her fear of social situations been present?

Less than 1 month	1-5 months	6 months or more
0	1	2

3.9 How old was s/he when this fear of social situations began? (if since birth, enter 0)

	years old

3.10 When [Name's] is in one of the social situations s/he fears, or when s/he thinks s/he is about come up against one of these situations, does s/he become anxious or upset

No	A little	A lot
0	1	2

3.12 3.11

3.11 How often does his/her fear of social situations result in him/her becoming upset like this?

Every now and then	Most weeks	Most days	Many times a day
0	1	2	3

3.12 Does his/her fear lead to [Name] avoiding social situations

No	A little	A lot
0	1	2

3.14 3.13

3.13 Does this avoidance interfere with his/her daily life?

No	A little	A lot
0	1	2

3.14 Does s/he think that this fear of social situations is over the top or unreasonable

No	Perhaps	Definitely
0	1	2

3.15 Is s/he upset about having this fear?

0	1	2

3.16 Has [Name's] fear of social situations put a burden on you or the family as a whole?

Not at all	A little	A medium amount	A great deal
0	1	2	3

SECTION 4 - Panic Attacks and Agoraphobia

Many children have times when they get very anxious or worked up about silly little things, but some children get severe panics that come out of the blue- they just don't seem to have any trigger at all.

4.1 In the **last 4 weeks**, has [Name] had a panic attack when s/he suddenly became very panicky for no reason at all, without even a little thing to set him/her off

No	Yes
0	1

4.2 Over the **last 4 weeks**, has [Name] been very afraid of, or tried to avoid, the following situations?

	No or Not Applicable	Yes
a) Crowds	0	1
b) Public Places	0	1
c) Travelling alone (If s/he ever does so)	0	1
d) Being far from home	0	1

If any of the items in 4.2 have been answered "Yes"' then continue with 4.3. Otherwise skip to section 5.

4.3 Do you think this fear or avoidance of (situation) is because s/he is afraid that if s/he had a panic attack, or something like that, s/he would find it difficult or embarrassing to get away, or wouldn't be able to get the help s/he needs?

No	Yes
0	1

SECTION 5 - Generalized Anxiety

This section is about worrying

5.1 Does [Name] ever worry?

No	Yes
0	1
↓ Section 6	↓ Continue

Some children worry about just a few things, sometimes related to specific fears, obsessions or separation anxieties. Other children worry about many different aspects of

their lives. They may have specific fears, obsessions or separation anxieties, but they also have a wide range of worries about many things.

5. 1a) Is [Name] a worrier in general?

No, s/he just has a few specific worries	Yes, s/he worries in general
0	1
Only continue if SDQ emotion score ≥3	*Continue*

5.2 Over the last **6 months**, has [Name] worried so much about so many things that it has really upset him/her or interfered with his/her life?

No	Perhaps	Definitely
0	1	2

If 5.2 = "Perhaps" or 5.2 = "Definitely" or SDQ emotion score is ≥3, then continue. If neither, then skip to section 6.

5.3 Over the **last 6 months,** and by comparison with other children of the same age, has [Name] worried about…

		No more than others	A little more than others	A lot more than others
a)	Past behaviour: Did I do that wrong? Have I upset someone? Have they forgiven me?	0	1	2
b)	School work, homework or examinations	0	1	2
c)	Disasters: Burglaries, muggings, fires, bombs etc.	0	1	2
d)	His/Her own health	0	1	2
e)	Bad things happening to others: family, friends, pets, the world (e.g. wars).	0	1	2
f)	The future: e.g. changing school, moving house, getting a job, getting a boy/girlfriend	0	1	2
g)	Making and keeping friends	0	1	2

h)	Death and dying	0	1	2
i)	Being bullied or teased	0	1	2
j)	His/Her appearance or weight	0	1	2
k)	Other specific worry (Describe)…… ……	0	1	2

If 2 or more of these worries are scored 'A lot more than others' then continue, else skip to Section 6.

5.4 Over the **last 6 months** has s/he worried excessively on more days than not?

No	Yes
0	1

5.5 Does s/he find it difficult to control the worry?

No	Yes
0	1

If neither 5.4= "yes" or 5.5 = "Yes", skip to section 6

If any of the following questions are answered "yes", ask* "Has this been true for more days than not in the last 6 months?" *and record answer in the second column.

5.6

		In general			More days than not in the last 6 months	
		No	Yes		No	Yes
a)	Does worrying lead to him/her feeling restless, keyed up, on edge, or unable to relax?	0	1	→	0	1
b)	Does worrying lead to him/her feeling tired or worn out more easily?	0	1	→	0	1
c)	Does worrying lead to difficulties in concentrating or his/her mind going blank?	0	1	→	0	1
d)	Does worrying lead to irritability?	0	1	→	0	1
e)	Does worrying lead to muscle tension?	0	1	→	0	1

f) Does worrying interfere with his/her sleep, e.g. difficulty in falling or staying asleep, or restless, unsatisfying sleep?

0	1	→	0	1

5.7 How upset or distressed is [Name] as a result of all his/her various worries?

Not at all	A little	A medium amount	A great deal
0	1	2	3

5.8 Have his/her worries interfered with….

	Not at all	A little	A medium amount	A great deal
a) how well s/he gets on with you and the rest of the family?	0	1	2	3
b) making and keeping friends?	0	1	2	3
c) learning or class work?	0	1	2	3
d) playing, hobbies, sports or other leisure activities?	0	1	2	3

5.9 Have these worries put a burden on you or the family as a whole?

Not at all	A little	A medium amount	A great deal
0	1	2	3

SECTION 6 - Depression

This section of the interview is about [Name's] mood.

6.1 In the **last 4 weeks**, have there been times when [Name] has been very sad, miserable, unhappy or tearful in a way that has been out of character for him/her?

No	Yes
0	1
↓	↓
6.7	6.2

6.2 Over the **last 4 weeks** has there been a period when s/he has been really miserable nearly <u>every</u> day

No	Yes
0	1

6.3 During the time when s/he has been miserable, has s/he been really miserable for most of the day? (i.e. for more hours than not)

No	Yes
0	1

6.4 When s/he has been miserable, could s/he be cheered up?

Easily	With difficulty/only briefly	Not at all
0	1	2

6.5 Over the **last 4 weeks**, the period of being really miserable has lasted:

Less than 2 weeks	2 weeks or more
0	1

6.7(Sic) In the **last 4 weeks**, have there been times when [Name] has been grumpy or irritable in a way that has been out of character for him/her?

No	Yes
0	1
↓ 6.13	↓ 6.8

6.8 Over the **last 4 weeks**, has there been a period when s/he has been really grumpy or irritable nearly every day?

No	Yes
0	1

6.9 During the time when s/he has been miserable, has s/he been grumpy or irritable for most of the day? (i.e. for more hours than not)

No	Yes
0	1

6.10 Has the irritability been improved by particular activities, by friends coming round, or by anything else?

Easily	With difficulty/only briefly	Not at all
0	1	2

6.11 Over the **last 4 weeks**, the period of being really irritable has lasted:

Less than 2 weeks	2 weeks or more
0	1

6.13 (Sic) In the **last 4 weeks**, have there been times when [Name] has lost interest in everything that s/he normally enjoys doing?

No	Yes
0	1
↓	↓

Skip rule at start of 6.18 6.14

6.14 Over the **last 4 weeks**, has there been a period when this lack of interest has been present nearly <u>every</u> day?

No	Yes
0	1

6.15 During these days when s/he has lost interest in things, has/he been like this for <u>most</u> of the day? (i.e. for more hours than not)

No	Yes
0	1

6.16 Over the **last 4 weeks**, this loss of interest has lasted:

Less than 2 weeks	2 weeks or more
0	1

Ask 6.17 ***if 6.1 <u>and</u> 6.2 <u>and</u> 6.3 = "Yes" OR if 6.7 <u>and</u> 6.8. <u>and</u> 6.9 = "Yes***

6.17 Has this loss of interest been present during the same period when s/he has been really miserable or irritable for most of the time

No	Yes
0	1

Ask 6.18 ***if 6.1 <u>and</u> 6.2 <u>and</u> 6.3 = "Yes" OR 6.7 <u>and</u> 6.8. <u>and</u> 6.9 = "Yes***
OR 6.13 <u>and</u> 6.14 = "Yes". Otherwise skip to 6.22. (** However, if unsure ask 6.18**)

6. 18 During the period when [Name} was sad, irritable or lacking in interest…….

		No	Yes
a)	Did s/he lack energy and seem tired all the time?	0	1
b)	Was s/he eating much more or much less than normal?	0	1
c)	Did s/he either lose or gain a lot of weight?	0	1
d)	Did s/he find it hard to get to sleep or to stay asleep?	0	1
e)	Did s/he sleep too much?	0	1
f)	Was s/he agitated or restless for much of the time?	0	1
g)	Did s/he feel worthless or unnecessarily guilty for much of the time?	0	1

		No	Yes
h)	Did s/he find it unusually hard to concentrate or think things out?	0	1
i)	Did s/he think about death a lot?	0	1
j)	Did s/he think about harming himself/herself or killing himself/herself?	0	1
k)	Did s/he try to harm himself/herself or kill himself/herself	0	1
l)	Over the whole of his/her lifetime, has s/he ever tried to harm himself/herself or kill himself/herself	0	1

6.19 How much has [Name's] sadness, irritability or loss of interest upset or distressed him/her

Not at all	A little	A medium amount	A great deal
0	1	2	3

6.20 Has his/her sadness, irritability or loss of interest interfered with….

		Not at all	A little	A medium amount	A great deal
a)	how well s/he gets on with you and the rest of the family?	0	1	2	3
b)	making and keeping friends?	0	1	2	3
c)	learning or class work?	0	1	2	3
d)	playing, hobbies, sports or other leisure activities?	0	1	2	3

6.21 Has his/her sadness, irritability or loss of interest put a burden on you or the family as a whole?

Not at all	A little	A medium amount	A great deal
0	1	2	3

Deliberate Self-Harm

6.22 Over the **last 4 weeks**, has s/he talked about deliberately harming or hurting himself/herself?

No	Yes
0	1

6.23 Over the **last 4 weeks**, has s/he tried to harm himself/herself?

No	Yes
0	1

6.24 Over the whole of his/her lifetime, has s/he ever tried to harm or hurt himself/herself?

No	Yes
0	1

SECTION 7- Attention and Activity

This section of the interview is about [Name's] level of activity and concentration over the **last 6 months**. Nearly all children are overactive or lose concentration at times, but what I would like to know is how [Name] compares with other children of his/her own age. I am interested in how s/he is usually – not on the occasional 'off day'.

7.1 Allowing for his/her age, do you think that [Name] definitely has some difficulties with overactivity or poor concentration?

No	Yes
0	1

If 7.1 = "yes" or if SDQ hyperactivity score is ≥4 then continue. If neither, then skip to section 8.

I would now like to go through some more detailed questions about how [Name] has usually been over the **last 6 months**. I will start with questions about how active s/he has been.

7.2 Over the **last 6 months,** and by comparison with other children his/her age…..	No more than others	A little more than others	A lot more than others
a) Does s/he often fidget?	0	1	2
b) Is it hard for him/her to stay sitting down for long?	0	1	2
c) Does s/he run or climb about when s/he shouldn't?	0	1	2
d) Does s/he find it hard to play or take part in other leisure activities without making a lot of noise?	0	1	2

e)	If s/he is rushing about, does s/he find it hard to calm down when someone asks him/her to?	0	1	2

The next few questions are about impulsiveness

7.3	Over the **last 6 months,** and by comparison with other children his/her age…..	No more than others	A little more than others	A lot more than others
a)	Does s/he often blurt out an answer before s/he heard the question properly?	0	1	2
b)	Is it hard for him/her to wait his/her turn?	0	1	2
c)	Does s/he often butt in on other people's conversations or games?	0	1	2
d)	Does s/he often go on talking if s/he has been asked to stop, or if no one is listening?	0	1	2

The next set of questions are about attention

7.4	Over the **last 6 months,** and by comparison with other children his/her age…..	No more than others	A little more than others	A lot more than others
a)	Does s/he often make careless mistakes or fail to pay attention to what s/he is supposed to be doing?	0	1	2
b)	Does s/he often lose interest in what s/he is doing?	0	1	2
c)	Does s/he often not listen to what people are saying to him/her?	0	1	2
d)	Does s/he often not finish a job properly?	0	1	2
e)	Is it often hard for him/her to get himself/herself organized to do something?	0	1	2
f)	Does s/he often try to get out of things s/he would have to think about, such as homework?	0	1	2
g)	Does s/he often lose things s/he needs for school or games?	0	1	2
h)	Is s/he easily distracted?	0	1	2
i)	Is s/he often forgetful?	0	1	2

M2J2) How often does his or her level of activity or his or her lack of attention lead to difficulties?

M2J3) How severe are the difficulties at their worst?

M2J4) How long has he or she been like this?

M2J5) Is his or her level of activity or his or her lack of attention interfering with his or her quality of life? If so, how?

M2J6) Have you tried to do anything about his or her overactivity, lack of attention or impulsiveness? If so, please describe what you've tried to do, any help that you have had, and whether this has made a difference?

		No more than others	A little more than others	A lot more than others
7.5	Have [Name's] teachers complained over the **last 6 months** of problems with…..			
a)	fidgetiness, restlessness or overactivity?	0	1	2
b)	poor concentration or being easily distracted?	0	1	2
c)	Acting without thinking about what s/he is doing, frequently butting in, or not waiting his/her turn?	0	1	2

If two or more of the items in 7.2, 7.3 or 7.4 have been answered "A lot more than others," then continue to 7.6. If not, skip to section 8.

		No	Yes
7.6	Have [Name's} difficulties with activity or concentration been there for at least **6 months**?	0	1

7.7			years old

How old was s/he when his/her difficulties with activity or concentration began?
(if since birth, enter 0)

7.8 How much have [Name's] difficulties with activity or concentration upset or distressed him/her?

Not at all	A little	A medium amount	A great deal
0	1	2	3

7.9 Have [Name's] difficulties with activity or concentration interfered with…..

	Not at all	A little	A medium amount	A great deal
a) how well s/he gets on with you and the rest of the family?	0	1	2	3
b) making and keeping friends?	0	1	2	3
c) learning or class work?	0	1	2	3
d) playing, hobbies, sports or other leisure activities?	0	1	2	3

7.10 Have these difficulties with activity or concentration put a burden on you or the family as a whole?

Not at all	A little	A medium amount	A great deal
0	1	2	3

SECTION 8-Awkward and Troublesome Behaviour

This next section of the interview is about behaviour. Nearly all children are awkward and difficult at times – not doing what they are told, being irritable or annoying, having temper outbursts, and so on. What I would like to know is how [Name] compares with other children of the same age. I am interested in how s/he is usually, and not just on occasional 'off days'.

8.1 Thinking about the **last 6 months**, how does [Name's] behaviour compare with other children of his/her age?

Less awkward or troublesome than average	About average	More awkward or troublesome than average
0	1	2

If 8.1 = "More awkward or troublesome than average", or if SDQ conduct problems score is ≥4, then continue. If neither, then skip to section 9

Some children are awkward or annoying with just one person – perhaps with yourself or just one brother or sister. Other children are troublesome with a range of adults or children. The following questions are about how [Name] is in general, and not just with one person.

		No more than others	A little more than others	A lot more than others
8.2	Over the **last 6 months**, and as compared with other children of the same age, has s/he often….			
a)	had temper outbursts?	0	1	2
b)	argued with grown-ups?	0	1	2
c)	taken no notice of rules, or refused to do as s/he is told?	0	1	2
d)	seemed to do things to annoy other people on purpose?	0	1	2
e)	blamed others for his/her own mistakes or bad behaviour?	0	1	2
f)	been touchy or easily annoyed?	0	1	2
g)	been angry and resentful?	0	1	2
h)	been spiteful?	0	1	2
i)	tried to get his/her own back on people?	0	1	2

If any of the items in 8.2 have been answered "A lot more than others", then continue with 8.3. If not, skip to 8.8.

		No	A little	A lot
8.3	Have [Name's] teachers complained over the **last 6 months** of problems with this kind of awkward behaviour or disruptiveness in class?	0	1	2

		No	Yes
8.4	Has [Name's} awkward behaviour been there for at least **6 months**?	0	1

8.5 How old was s/he when this sort of awkward behaviour began? (if since birth, enter 0) [ ] years old

8.6	Has [Name's] awkward behaviour interfered with…..	Not at all	A little	A medium amount	A great deal
a)	how well s/he gets on with you and the rest of the family?	0	1	2	3
b)	making and keeping friends?	0	1	2	3
c)	learning or class work?	0	1	2	3
d)	playing, hobbies, sports or other leisure activities?	0	1	2	3

8.7	Has his/her awkward behaviour put a burden on you or the family as a whole?	Not at all	A little	A medium amount	A great deal
		0	1	2	3

Continue with 8.8.

Behaviour that sometimes gets children into trouble.

I'm now going to ask about behaviour that sometimes gets children into trouble, including dangerous, aggressive or antisocial behaviour. Please answer according to how s/he has been over the last year – I'm switching to the last 12 months for this next set of questions.

If any of the following questions are answered* "Definitely" *ask* "Has this been going on for the last 6 months?" *and record answer in the second column.

8.8	As far as you know, over the **last 12 months**…	Over the last 12 months			Last 6 months	
		No	Perhaps	Definitely	No	Yes
a)	has s/he often told lies in order to get things or favours from others, or to get out of having to do things s/he is supposed to do?	0	1	2	→ 0	1

8.8	As far as you know, over the **last 12 months**…	Over the last 12 months				Last 6 months	
b)	has s/he often started fights? (Other than with brothers and sisters)	0	1	2	→	0	1
c)	has s/he often bullied or threatened people?	0	1	2	→	0	1
d)	has s/he often stayed out after dark much later than s/he was supposed to?	0	1	2	→	0	1
e)	has s/he stolen from the house, or from other people's houses, or from shops or school? (This doesn't include very minor thefts e.g. stealing his/her brother's pencil or food from the fridge)	0	1	2	→	0	1
f)	has s/he run away from home more than once, or ever stayed away all night without your permission?	0	1	2	→	0	1
g)	has s/he often played truant (bunked off) from school?	0	1	2	→	0	1

Only continue with 8.9 if any of the items in 8.2 have been answered "A lot more than others", or any of the items in 8.8 have been answered "Definitely" otherwise skip to section 9

May I now ask you about a list of less common but potentially more serious behaviours? I have to ask all people all questions even when they are not likely to apply.

*If any of the following questions are answered "Yes" then ask "*Has this happened in the **last 6 months**?*" and record answer in second column*

8.9	As far as you know, have any of the following happened even once in the **last 12 months**?	***Over the last 12 months***		***Last 6 months***	
		No	Yes	No	Yes

		Over the last 12 months			***Last 6 months***	
8.9	As far as you know, have any of the following happened even once in the **last 12 months**?					
a)	Has s/he used a weapon or anything that could seriously hurt someone? (*e.g. a bat, brick, broken bottle, knife, gun*)	0	1	→	0	1
b)	Has s/he really hurt someone or been physically cruel to them (*e.g. has tied up, cut or burned someone*).	0	1	→	0	1
c)	Has s/he been really cruel on purpose to animals and birds	0	1	→	0	1
d)	Has s/he deliberately started a fire? (*This is only if s/he intended to cause severe damage. This question is not about lighting campfires, or burning individual matches or pieces of paper*)	0	1	→	0	1
e)	Has s/he deliberately destroyed someone else's property? (*This question is not about fire setting or very minor acts e.g. destroying sister's drawing. It does include behaviour such as smashing car windows or school vandalism*)	0	1	→	0	1
f)	Has s/he been involved in stealing on the streets, e.g. snatching a handbag or mugging?	0	1	→	0	1
g)	Has s/he broken into a house, any other building or a car?	0	1	→	0	1

8.10	Have [Name's] teachers complained of troublesome behaviour over the **last 6 months**?	No	Yes
		0	1

8.10 A	Has his/her troublesome behaviour been present for at **least 6 months?**	No	Yes
		0	1

8.10	Has [Name] ever been in trouble with the police? (*Describe*)	No	Yes

…… ……	0	1

If any items in 8.8 have been ticked "Definitely" or items in 8.9 answered "Yes", then continue. Otherwise skip to section 9

8.11 Has [Name's] troublesome behaviour interfered with….

		Not at all	A little	A medium amount	A great deal
a)	how well s/he gets on with you and the rest of the family?	0	1	2	3
b)	making and keeping friends?	0	1	2	3
c)	learning or class work?	0	1	2	3
d)	playing, hobbies, sports or other leisure activities?	0	1	2	3

8.12 Has his/her troublesome behaviour put a burden on you or the family as a whole?	Not at all	A little	A medium amount	A great deal
	0	1	2	3

SECTION 9- Strengths

I have been asking you a lot of questions about difficulties and problems. I now want to ask you about (Child's) good points or strengths.

9.1	**Do the following descriptions apply to him/her?**	No	A little	A lot
a)	Generous	0	1	2
b)	Lively	0	1	2
c)	Keen to learn	0	1	2
d)	Affectionate	0	1	2
e)	Reliable and responsible	0	1	2
f)	Easy going	0	1	2
g)	Good fun, good sense of humour	0	1	2

9.1	**Do the following descriptions apply to him/her?**	No	A little	A lot
h)	Interested in many things	0	1	2
i)	Caring, kind hearted	0	1	2
j)	Bounces back quickly after setbacks	0	1	2
k)	Grateful, appreciative of what s/he gets	0	1	2
l)	Independent	0	1	2

9.2	**What are the things s/he does that really please you?**	No	A little	A lot
a)	Helps around the home	0	1	2
b)	Gets on well with the rest of the family	0	1	2
c)	Does homework without needing to be reminded	0	1	2
d)	Creative activities: art, acting, music, making things	0	1	2
e)	Likes to be involved in family activities	0	1	2
f)	Takes care of his/her appearance	0	1	2
g)	Good at school work	0	1	2
h)	Polite	0	1	2
i)	Good at sport	0	1	2
j)	Keeps his/her bedroom tidy	0	1	2
k)	Good with friends	0	1	2
l)	Well behaved	0	1	2

9.3 Does [Name] have any other good points you particularly want to mention?

……

……

APPENDIX C: CONSENT FORMS FOR THE 4.5-YEAR FOLLOW-UP

Canterbury Child Development
Research Group
Department of Psychology
College of Science

November 2007

CODE NUMBER

4.5-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, 2007.

- 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 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**: _____