



Early inhibitory control and working memory abilities of children prenatally exposed to methadone

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ABSTRACT

Background: Methadone maintenance is the most common method of treating opioid-dependent pregnant women. However, little is known about the impact of prenatal methadone exposure on child neurocognitive development.

Aims: To examine the early executive functioning of children born to methadone-maintained mothers, and to assess relations between executive functioning and later emotional and behavioral adjustment.

Study design: Prospective longitudinal study.

Participants: The sample consisted of 68 methadone-exposed children and 88 non-methadone-exposed children.

Outcome measures: At age 2 years, children's inhibitory control and working memory were assessed using the Snack Delay and Three Boxes tasks. At 2 and 4.5 years, their emotional and behavioral adjustment was assessed using the caregiver-completed Strengths and Difficulties Questionnaire.

Results: Methadone-exposed children had poorer inhibitory control than non-exposed children ($p < 0.0001$). These differences were explained by maternal education and prenatal benzodiazepine use. With respect to working memory, although both groups performed similarly on the first trial set, non-exposed children significantly improved their performance on the second trial set ($p = 0.002$), while methadone-exposed children did not ($p = 0.92$). Inhibitory control at age 2 years was predictive of higher conduct ($p = 0.001$), hyperactivity ($p = 0.0001$), peer relationship ($p = 0.02$), and total ($p < 0.0001$) problems at 4.5 years even after adjustment for behavioral problems at 2 years.

Conclusions: Methadone-exposed children demonstrate difficulties with inhibitory control and possibly sustained attention/learning. These difficulties were explained by factors correlated with maternal prenatal methadone use. Longer-term follow-up of these children is needed to understand the effects of prenatal methadone exposure and related maternal factors on executive functioning and behavioral adjustment.

1. Introduction

Substitution treatment with methadone, a synthetic opioid analgesic, is the current standard of care for opioid-dependent pregnant women [1]. It has important benefits over illicit opioid use, including more stable maternal blood drug levels, improved prenatal care attendance, and reduced withdrawal and drug-seeking [1]. Maternal methadone maintenance treatment also has clear advantages for infants, including reduced fetal distress, miscarriage, growth restriction, and preterm birth [2]. However, maternal prenatal methadone use may not be without risks for infant development. These potential risks are especially relevant given recent population increases in opioid use and abuse during pregnancy [3].

Existing outcome studies have focused primarily on the neonatal

period. Compared to non-exposed infants, methadone-exposed infants are born earlier, smaller [4], and at high risk of neonatal abstinence syndrome (50–90%) [5]. There is also suggestion of altered neurological development. Animal studies report reduced cell proliferation and myelination, and neurochemical alterations in the hippocampus, striatum, and forebrain [6,7]. Volumetric MRI studies in methadone-exposed infants ($n = 16$) and school-aged children ($n = 10$) found reduced total brain and basal ganglia volumes at birth [8], and smaller total brain and white matter volumes in childhood [9]. A diffusion tensor imaging study of 13 methadone-exposed and 7 non-exposed infants found higher mean diffusivity in the superior longitudinal fasciculus, suggesting altered white matter microstructural development [10]. These findings raise important questions regarding the impact of prenatal methadone exposure on child cognitive development.

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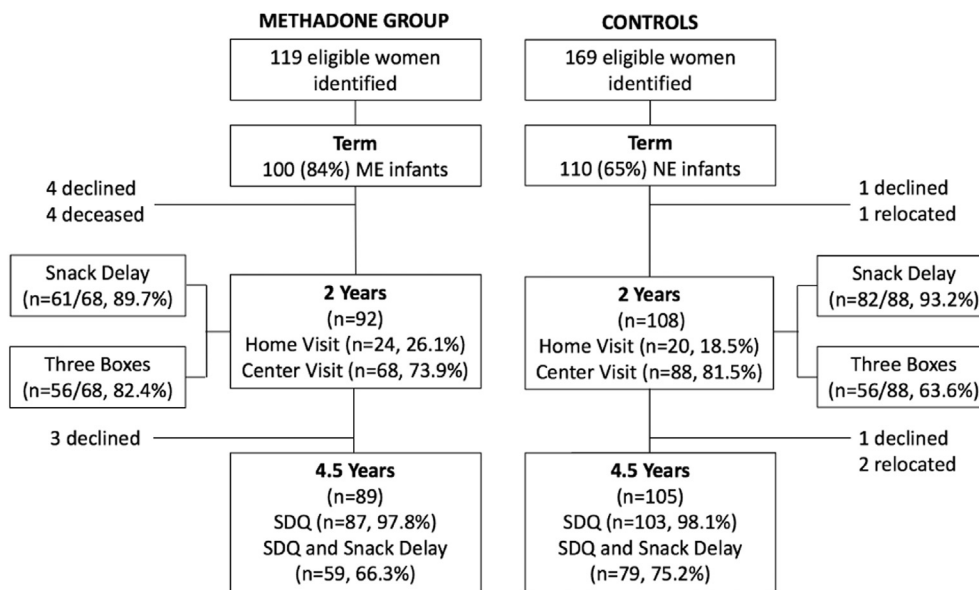


Fig. 1. Study design.

However, there are virtually no contemporary studies examining the cognitive outcomes of methadone-exposed children. Existing studies were primarily conducted in the 1980s and 1990s. Results indicate that methadone-exposed children perform less well than non-exposed children on global measures of cognition [11] and intelligence [12,13]. However, scores often fall in the normal range [11,14]. For example, Rosen et al. found that methadone-exposed children had lower scores on the Bayley Scales of Infant Development at ages 12 and 18 months than non-exposed children [13].

While these data suggest possible adverse cognitive effects associated with prenatal methadone exposure, several limitations should be noted. These include small sample sizes [15,16], no or small control groups [11,15–17], high attrition [11,13,18], cross-sectional design [16], inadequate specification of type or dose of opioid exposure [12,15,17,19], use of unblinded examiners [15,16,18,20], reliance on self-report for maternal drug use [20], and no/inadequate control for confounding factors such as polysubstance use, maternal nutrition, mental health, and socioeconomic adversity [15,16,18,21]. Studies have also almost exclusively focused on general cognition and intelligence [11,14,21], despite other prenatal drug exposure studies suggesting that subtle neuropsychological impairments may be present even in the absence of global cognitive delay [22].

One such important set of neurocognitive skills that has received scant attention in relation to prenatal methadone exposure is executive functioning, which includes behavioral control, working memory, and cognitive flexibility [23]. These abilities begin to emerge during infancy, develop until early adulthood [24], and are predictive of later adverse behavioral and academic outcomes [25]. Two of the earliest executive functioning skills to develop are inhibitory control and working memory. Inhibitory control involves the voluntary, effortful regulation of avoidance and approach processes [26], while working memory involves the temporary storage and manipulation of information necessary for cognitive tasks [27].

There is considerable overlap between brain regions and networks involved in executive functioning (e.g., prefrontal cortex, parietal cortex, anterior cingulate gyrus) [28] and regional alterations observed in opioid-exposed infants and children [8–10]. However, data regarding the effects of prenatal methadone exposure on children's executive functioning are limited to a single study showing that methadone- or buprenorphine-exposed children performed less well than control children on two inhibitory control tasks [19]. Performance differences were explained by maternal employment and education, suggesting that executive difficulties may reflect the effects of correlated maternal

factors. There is a need for further research to confirm these preliminary observations, assess whether these differences might be detectable at earlier ages, and determine whether early executive difficulties may be predictive of later problems.

Accordingly, the primary aim of this study was to compare the inhibitory control and working memory abilities of methadone-exposed and non-exposed children at age 2 years. Second, the extent to which between-group differences in executive functioning reflect the direct effects of prenatal methadone exposure or other factors correlated with maternal methadone treatment was examined. Finally, the extent to which early executive functioning might place children at increased risk of emotional and behavioral problems at 4.5 years was assessed.

2. Methods

2.1. Participants

The study sample included two groups of children whose mothers were recruited during their second/third pregnancy trimester or at birth in Christchurch, New Zealand from 2003 to 2008 [29]. Exclusion criteria included maternal inability to give informed consent, HIV diagnosis, delivery outside the region, very preterm birth (≤ 32 weeks' gestation), suspected fetal alcohol syndrome, or congenital abnormalities. Fig. 1 provides an overview of the study design and sample recruitment/retention to age 4.5 years.

2.1.1. Methadone-exposed group

The first group comprised a consecutive series of 100 infants born to opioid-dependent women in methadone maintenance treatment during pregnancy. Over the recruitment period, 119 women and infants were eligible. Of these, 99 women were recruited (83%), resulting in 100 live births (58 male, one set of twins). Reasons for non-recruitment included failure to recruit ($n = 2$) and declined ($n = 17$). Of those recruited, almost two-thirds (62%) were engaged in methadone treatment at the time of pregnancy, with 94% enrolled by the end of their second trimester. During pregnancy, treatment was provided by a specialist service within the Christchurch Methadone Program in partnership with Christchurch Women's Hospital. The mean maternal methadone dose in the third pregnancy trimester was 64.9 mg (range: 12.5–195.0 mg), and the mean maternal methadone dose across pregnancy was 62.4 mg (range: 6.7–195.0 mg). At age 2 years, 4 (4%) children had died and 4 (4%) families declined to participate, resulting in a sample of 92 (92%) methadone-exposed children (see Fig. 1). Of these, 22 (23.9%) had

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