**ABSTRACT**

**Objective:** This paper examines the school readiness of a regional cohort of prenatally methadone-exposed children across five outcome domains and examines factors contributing to impairment risk.

**Method:** A sample of 100 children born to women in methadone maintenance treatment and 110 randomly identified non-methadone-exposed children were studied from birth to age 4.5 years. At 4.5 years, children underwent comprehensive assessment of their physical/motor development, social-emotional skills, approaches to learning, language, and cognitive functioning. Predictors of children’s overall school readiness were examined, including the extent of prenatal substance exposure and social risk, maternal mental health, infant clinical factors, and the total score from the Home Observation Measurement of the Environment (HOME) scale administered at 18 months.

**Results:** Methadone-exposed children had higher rates of delay/impairment across all outcome domains (ORs 4.0–5.3), with 72% impaired in at least one domain. Multiple problems were also common, affecting 48% of methadone-exposed children compared with 15% of control children. The mean number of school readiness domains impaired increased with increasing prenatal substance exposure (rate ratio [RR] =1.05 [1.01–1.11]), higher social risk (RR = 1.35 [1.20–1.53]), male sex (RR = 1.69 [1.27–2.25]), and lower HOME scores indicating a poorer quality postnatal environment (RR = 0.96 [0.94–0.99]).

**Conclusions:** Children born to opioid-dependent mothers are at high risk of impaired school readiness, with problems in multiple domains common. Impaired school readiness was associated with greater maternal substance use, higher social risk, male sex, and lower quality caregiving environments.

**Key terms:** Opioid, methadone, substance use, child outcome, neurodevelopment.

**Health and Neurodevelopment of Children Born to Opioid Dependent Mothers at School Entry**

Opioid use during pregnancy has increased dramatically in recent years and is now a major public health problem.1 For these women, the most common management approach is methadone maintenance treatment (MMT)which reduces maternal craving and withdrawal, and results in improved antenatal care and an increased likelihood of a term delivery.Nonetheless, relative to the general population, infants born to women in MMT remain at increased risk of preterm birth, growth restriction and neonatal opioid withdrawal syndrome (50–80%).2 However, limited contemporary data exist that describe their longer-term outcomes. As a result, these high-risk children are not routinely included in follow-up and monitoring programs.

We adopt a school readiness framework to assess the health and neurodevelopmental outcomes of a regional cohort of methadone-exposed (ME) and non-ME comparison children at school entry. Five readiness domains identified by the American Academy of Pediatrics (AAP) were examined, including 1) physical well-being and motor development, 2) social-emotional skills, 3) approaches to learning, 4) language development, and 5) cognition and general knowledge.3 To date, no study has examined opioid-exposed children’s development across all of these domains, or documented the extent of comorbid impairments in multiple domains. This latter issue is very important since multiple domain impairments suggest greater neurodevelopmental disturbance and a worse long-term prognosis.4 The little data that do exist is limited by the use of global measures of development (e.g., Bayley Scales), short term follow-up (i.e., infancy) and poor sample retention (55–65%) which compromises generalizability.5-7

Nonetheless, with these limitations in mind, data suggest that children born to opioid-dependent mothers have higher rates of early vision problems8 and psychomotor impairment than non-exposed children.5, 9 Non-compliant and inattentive/hyperactive behavior also appear more common.7, 9, 10 Little is known about their approaches to learning and executive functioning, although there is some suggestion of increased inhibitory control difficulties during early childhood.11, 12 Finally, prenatal opioid-exposure has been linked with poorer receptive and expressive language skills by age 3 years.5, 7

In contrast, results are more mixed for cognitive outcomes. But, in general, ME children tend to perform within the normal range on standardized general cognition and IQ measures, although their total scores are, on average, lower than the scores of non-exposed children’s.5, 7, 11 Several reasons may account for the variability in findings across studies. First, methadone doses, in addition to the extent of other opioid and substance exposures, were not always reported in early studies. Methadone doses/concentrations have also changed over time, with more contemporary samples typically being exposed to higher doses.Second, studies have varied considerably in the measure/s (and criteria) used to define delay or impairment. Third, few studies have included a comparison control group in their design making them highly reliant on test norms which are susceptible to the Flynn effect. This occurs when test norms become outdated over time due to a gradual increase in the ability of the general population. Of the few studies that have included a comparison group, most have tended to match on selected pregnancy and socioeconomic factors.5, 6 Whilst this approach is helpful in controlling for key factors known to be associated with maternal opioid use/treatment, it can also introduce unintended, potentially unknown, biases.13 Even more importantly from a public health perspective, this approach also likely underestimates the true population risks associated with maternal opioid use during pregnancy, as well as the clinical needs of this vulnerable group of children and their families. Thus, there are clear methodological advantages in recruiting a representative regional comparison group and then controlling for correlated confounding factors in analyses, if the goal is understanding the full extent of clinical risk and public health burden. Fourth, studies vary in their consideration of confounding maternal (social adversity, mental health) and pregnancy-related (substance use, nutrition, prematurity) factors, with some including a wide range of potential covariates,10 and others simply reporting descriptive outcome data.5 Finally, with a few exceptions,10 few studies have considered the contributions of the postnatal family environment to later child risks. Yet an improvedunderstanding of these processes alongside early biological risk factors is likely to be helpful for both intervention and prevention planning.

Thus, the aims of this study were:

1. To describe the health and neurodevelopmental functioning of ME and non-ME children at age 4.5 years on measures assessing the five AAP school readiness domains. Also of interest was the extent of multiple domain impairments.
2. To examine the risk factors and life course processes that increased the likelihood that children would not be ready for school by late preschool age. Risk factors of interest spanned maternal, child, and family pre and postnatal characteristics.

**METHODS**

**Participants**

Participants were drawn from a prospective longitudinal study of two groups of children born between 2003 and 2008 at Christchurch Women’s Hospital. This single birth facility is the largest maternity care provider in the Canterbury region of New Zealand, and is the only hospital in the region with an antenatal obstetric team that works in partnership with the Christchurch Methadone Programme. For both groups, mothers were recruited during their third trimester of pregnancy or at birth. Exclusion criteria included very preterm birth (≤ 32 weeks), congenital abnormality, HIV, fetal alcohol syndrome, and non-English speaking.

The first group comprised a consecutive series of 100 children who were born to opioid-dependent mothers enrolled in MMT during pregnancy. Figure 1 provides an overview of the recruitment and retention of this group over the study period. As shown, excluding deaths (5 stillbirths), 120 mothers were eligible for inclusion in the study. These mothers gave birth to 121 children (including one set of twins). Of these, 99 mothers and 100 infants were successfully recruited, representing 83% of all ME infants born in the region during that time period. Reasons for non-recruitment included declined participation (n=19) and missed recruitment (n=2). Among the recruited mothers, 76% were enrolled in MMT by the end of their first trimester, and 95% were enrolled by the second trimester. The ME group had 89% retention to age 4.5 years. Reasons for sample loss to age 4.5 years included infant death (n=4) and declined participation (n=7).The mean third trimester methadone dose for the mothers of these 89 children was 65.0 ± 32.5 mg/day (range 12.5–195.0). The majority (87.6%) of these children were treated for neonatal opioid withdrawal at birth. Treatment with morphine commenced if the infant had three Finnegan scores of eight or higher, with Finnegan assessments conducted every 4 hours.

The second group comprised 110 non-ME comparison children who were identified at random from the hospital delivery schedule over the same birth period. As shown in Figure 1, 169 pregnant comparison women were identified and approached based on their expected due dates. Reasons for non-recruitment included declined participation (n=41) and inability to trace at term (n=20). This resulted in 108 comparison mothers and 110 non-ME infants who were enrolled in the study, including two sets of twins. Comparison of the socioeconomic profile of these families with regional census data showed that they were representative of families living in the region. Retention to age 4.5 years was 95%. Reasons for sample loss to age 4.5 years included declined participation (n=2), and relocation overseas (n=3). Two additional children, one with a chromosomal microdeletion and both with severe neurodevelopmental delay, were unable to be tested.

Table 1 provides a descriptive profile of the two study groups. Further details about maternal substance use during each pregnancy trimester is provided in Supplemental Table 1 and in an earlier publication.14

**Procedure**

Data were collected at three time points: late pregnancy/birth, 18 months, and 4.5 years. During the third trimester or at birth, a senior research nurse specialist interviewed all of the mothers about their socioeconomic circumstances, mental health, pregnancy nutrition and substance use/dependence. Random maternal urine samples were collected across the pregnancy, and then an infant meconium sample was also collected at birth. At infant age 18 months, an observation of the quality of the postnatal environment was conducted during a home visit assessment. At age 4.5 years, children and parents were then invited to attend a half day neurodevelopmental follow-up assessment that included a comprehensive evaluation of each child’s school readiness across five neurodevelopmental domains. All child measures were administered by research staff who were blinded to study group and maternal substance use and psychosocial history, with the exception of the maternal psychosocial interview. Written informed consent was obtained from mothers or primary caregivers at every assessment point, with all measures and procedures approved by the Upper South B Regional Ethics Committee, Canterbury, New Zealand (Ref: URB/07/10/042). Below is a description of our major outcome measures at age 4.5 years, followed by a description of predictors collected during pregnancy/at birth, and at 18 months.

**Measures**

School Readiness at Age 4.5 Years.

*Physical well-being and motor development* was assessed using direct assessment and parent/caregiver report. First, visual-motor skills were directly assessed using the Beery-Buktenia Developmental Test of Visual-Motor Integration, 5th Edition. This standardized measure assessed children’s ability to re-create increasingly difficult geometric shapes using a pencil and paper. The test is internally consistent and has good concurrent and predictive validity.15 A clinician’s assessment was not part of the study protocol, therefore we drew on two parent-reported development and health outcomes as indicators of poor readiness to learn at school: toilet training and oral health. Children were defined as “not ready” in this domain if their Beery score was below the 10th percentile of the comparison group mean, they had any teeth removed due to decay before age 4.5 years, and/or they wet or soiled their pants most days.

*Social-emotional skills* were assessed using the caregiver-completed Strengths and Difficulties Questionnaire (SDQ). This 25-item questionnaire measured children’sprosocial behaviour as well as their emotional, conduct, inattention/hyperactivity, and peer problems.Items across these four subscales were then summed to form a total problems score. The SDQ is a well-validated screening measure with good test-retest reliability.16 Children were defined as “not ready” in this domain if their total problems score was above the 10th percentile of the comparison group mean.

*Approaches to learning* was assessed using the Phelps Kindergarten Readiness Scale II which measures verbal, perceptual, auditory, and overall information processing.17 This test has good predictive validity.18 Children were defined as “not ready” in this domain if their total score was below the 10th percentile of the comparison group mean.

*Language development* was assessed using the internally consistent Clinical Evaluation of Language Fundamentals – Preschool.19 Six subtests were administered to assess children’s receptive (three subtests) and expressive (three subtests) language skills, providing a total language score. Children were defined as “not ready” in this domain if their total language score was below the 10th percentile of the comparison group mean.

*Cognition and general knowledge* was assessed using a short form of the Wechsler Preschool and Primary Scales of Intelligence Revised.20 This consisted of two performance (Block Design and Picture Completion) and two verbal subtests (Arithmetic and Comprehension). Scores from the short form of the WPPSI-R correlate highly with full-scale scores (*r* = .92).21 Children were defined as “not ready” in this domain if their full scale IQ was below the 10th percentile of the comparison group mean.

*Overall School Readiness* was estimated by summing the total number of domains in which children demonstrated delay/impairment. As described, delay/impairment in each domain was computed using the 10th percentile score of the non-ME control group. The use of a cut-point based on a representative control group is a widely used approach that helps to minimize the Flynn Effect and the under- or over-identification of children at risk due to the use of non-local international test norms.4, 22 In general, with the exception of the WPPSI-R, cut-points based on our control group corresponded very closely to test norms. For the overall school readiness variable, higher scores indicated lower levels of school readiness.

Maternal Pregnancy/Birth Characteristics

*Maternal pregnancy substance use.* There were three independent measures of maternal substance use during pregnancy, including a maternal interview, random maternal urine sampling, and infant meconium sampling. First, substance use was assessed as part of a comprehensive maternal interview completed in the late third trimester or at birth. Detailed information was collected about the frequency and duration of tobacco, alcohol, marijuana, benzodiazepine, stimulant, and other opioid use for each pregnancy trimester. Second, over the course of pregnancy the women in the methadone group provided random urine samples to Community Alcohol and Drug Services, which were analysed for other illicit substance use. Finally, meconium samples were collected from 81% of ME and 46% of comparison infants at birth. Collection of the comparison infants’ meconium was made more difficult due to their earlier hospital discharge compared to the ME infants. We appreciate that this was not ideal, but this sub-sample was deemed sufficient to assess reliability of maternal self report data. Thus, results from the maternal urine and infant meconium analysis after birth were used to cross-check self-reported use of marijuana, benzodiazepines, stimulants, other opioids, and antidepressants. This analysis showed strong concordance between self-report and toxicological data sources (>80%).

In the current study, between-group comparisons were first made using our group variable defined on the basis of maternal methadone treatment during pregnancy. When examining other/polysubstance exposures in multivariate analysis, we used a prenatal substance exposure variable that reflected the number of different substances (including methadone/opioids) mothers used during pregnancy, as well as the amount of each substance used across pregnancy. We chose this approach because multiple substance use is common in opioid-dependent mothers, and because a greater extent of prenatal substance exposure has previously been associated with poorer neurodevelopmental outcomes. The summative prenatal exposure variable was based on the mothers self-reports, their urine sample analyses, and their infant’s meconium, and calculated as follows: a) third trimester methadone dose was coded into four categories (none, low dose (≤50mg/day), moderate dose (50–79mg/day), and high dose (≥80 mg/day); b) smoking across pregnancy was coded into three categories (none, 1–9 cigarettes per day, ≥10 per day; c) alcohol use across pregnancy was coded into four categories (none, <1 drink per week, 1–5 drinks per week, >5 drinks per week); d) marijuana use across pregnancy was coded into three categories (none, 1–2 joints per week, ≥3 joints per week), e) benzodiazepine use across pregnancy was coded into three categories (none, 1–2 times per week, ≥3 times per week), f) stimulant use was coded into three categories (none, 1–2 times per week, ≥3 times per week), and g) antidepressant use was coded into two categories (none, any use).

*Maternal pregnancy nutrition* was estimated based on the average total number of servings of fruit, vegetables, meat, bread, other cereals, milk and egg consumed per week.

Five *socioeconomic background* measures were collected. These included: 1) early motherhood (< 21 years); 2) single parent (not married/cohabiting); 3) minority ethnicity (Māori, Pacific Islander, Asian or African); 4) maternal educational underachievement (did not complete high school); and 5) low socioeconomic status (unemployed, semi/unskilled).23 A composite measure of Social Risk was created that was a summative index of these five dichotomous (0=no/1=yes) maternal social risk indicators.

*Maternal depression at birth* was measured using the Edinburgh Postnatal Depression Scale (EPDS). Mothers responded to 10 statements regarding their depressive symptomology over the previous 2 weeks.24 Item responses ranged between: (0) often, (1) sometimes, (2) hardly ever, and (3) never. A cut-off score of ≥ 13 on the EPDS is reported to have adequate sensitivity (79%) and specificity (85%) for identifying depression.

Neonatal Measures

Extensive infant clinical data were recorded from hospital records including sex, gestational age at birth, and birth weight, length and head circumference. The latter three growth parameter measurements were transformed into z-scores that adjusted for infant sex and gestational age.

Postnatal Environment

The quality of the early caregiving environment was assessed using the infant-toddler version of the Home Observation for Measurement of the Environment (HOME) inventory,25 completedduring a home visit at age 18-months. The HOME comprised of 45 items, with six subscales: (1) emotional and verbal responsivity of the caregiver, (2) acceptance of suboptimal behaviour and avoidance of restriction and punishment, (3) organisation of the physical and temporal environment, (4) provision of appropriate play materials, (5) parental involvement with the child, and (6) opportunities for variety in daily stimulation. Total HOME scores, calculated by summing each of the six subscale scores, were used in the current analyses, with higher scores indicating a more stimulating and supportive caregiving environment. The HOME inventory has good psychometric properties, with high internal consistency of the total score (α = .80) and inter-observer reliability consistently reported as .80 or more.26

**Statistical Analyses**

Between-group differences on the predictors and on measures of children’s school readiness at age 4.5 years were analyzed using *t-*tests for independent means and chi-square tests of independence, with Cohen’s *d* or odds ratios giving a measure of effect size. Overall school readiness was a count variable comprised of the total number of domains in which children demonstrated delay/impairment. Poisson regression analyses were conducted to predict the number of school readiness domains impaired based on the independent predictors prenatal substance exposure, maternal social risk, depression during pregnancy, infant clinical factors, and the quality of the postnatal caregiving environment. A rate ratio (RR) is provided for each predictor, which is the exponentiated value of its coefficient. The RR can be converted to a percentage with, for example, an RR of 1.10 for a continuous variable indicating a 10% percent increase in the mean number of school readiness impairments associated with every unit increase in that predictor. For a dichotomous predictor, an RR of 1.10 would indicate a 10% increase in the mean number of school readiness impairments for the group/category of interest, relative to the reference category.

**RESULTS**

**Neurodevelopmental Impairment at Age 4.5 Years**

Table 2 shows ME and comparison children’s functioning across each of the five school readiness domains.

Visual-motor Development and Physical Well-being. ME children’s mean visual-motor integration score was 0.8 SDs below that of comparison children’s. They were twice as likely to be incontinent, with over 1 in 10 soiling or wetting most days (OR=2.7 [1.0 – 7.6]). Serious dental decay was also more common (OR=7.1 [1.5 – 33.2]). Overall, ME children were 3 times more likely to be physically not school ready (48% v. 16%, OR=5.1 [2.5 – 9.8]).

Social-emotional Skills. ME children obtained emotional, conduct, inattention/hyperactivity, and peer problems scores that were 0.4 to 1.0 SDs higher than the scores of comparison children. They were over 3 times more likely to be impaired in this domain (33% v. 9%, OR=5.1 [2.3–11.6]).

Approaches to Learning. ME children performed less well than non-ME children on verbal, auditory, and perceptual processing, scoring 0.6 to 0.8 SDs lower on all subtests of the PKRS-II. Based on their total score, ME children were 3 times more likely than comparison children to be impaired in this domain (38% v. 12%, OR=4.5 [2.2–9.5]).

Language Development. ME children’s mean receptive and expressive language scores were 1 SD below comparison children’s and they were 3 times more likely to be impaired in this domain (33% v. 11%, OR=4.0 [1.9–8.7]).

Cognition and General Knowledge. Finally, the ME group’s mean IQ score was 1 SD below the comparison group’s, with ME children being 3 times more likely to be not school ready in their general cognitive functioning (39% v. 13%, OR = 4.5 [2.2–9.2]).

**Extent of Comorbid School Readiness Impairment**

Less than a third of ME children were free of any school readiness domain impairments by age 4.5 years (28% v. 71%, see Table 3). Multiple domain impairments were common, with almost half (48%) of ME children subject to impairments in two or more domains compared with 15% of non-ME children (χ2linear trend=38.8, *p*<.001). ME children’s rates of impairment were 3.2 times higher than comparison children’s (95% CI, 2.1–4.9), with the mean number of domains impaired for ME children being 1.9, compared to 0.6 for the non-ME children in the control group.

**Maternal, Child and Family Predictors of School Readiness by Age 4.5 Years**

The above results suggest that children born to mothers in MMT are at increased risk for a range of problems when compared with a group of randomly identified non-ME comparison children. Thus, Poisson regression analyses were used to identify the key factors that placed study children at increased risk of not being ready for school. Children from both groups were included in this analysis, with the results for all variables included in the model shown in Table 4.

As shown, four factors were found to independently predict the extent of children’s school readiness problems in this sample. These included the overall extent of prenatal substance exposure (RR=1.05 [1.01–1.11]), family social risk (RR=1.35 [1.20–1.53]), male sex (RR=1.69 [1.27–2.25), and the quality of the postnatal environment (RR=0.97 [0.94–0.99]). In contrast, holding all other factors constant, high maternal depressive symptoms at birth, and gestational age did not add to the prediction of child school readiness. These results suggest that male children born to mothers from high risk social backgrounds who took substances during pregnancy and then provided poorer quality care and home environments for their children were at greatest risk of having high rates of health and neurodevelopmental problems that meant they were ill prepared or not ready for the learning and behavioural demands of the school environment.

**DISCUSSION**

This study examined the neurodevelopmental functioning of children born to mothers enrolled in MMT during pregnancy. Five domains of school readiness were assessed, including physical well-being and visual-motor development, social-emotional skills, approaches to learning, language, and general cognition.

Findings showed that children born to opioid-dependent mothers in MMT are at very high risk of health and neurodevelopmental impairments that will likely impact their transition to school, educational achievement, and life course outcomes. They had higher rates of incontinence, dental decay, information processing problems, and mental health difficulties spanning emotional, conduct and hyperactivity/inattention problems. Consistent with limited existing data, they also had poorer visual-motor integration abilities,9 and lower receptive and expressive language abilities.5, 7 Similar to older, less well-controlled studies, their IQ scores were lower than non-ME children’s, with most scoring in the low-average range.5, 7

Further examination of the extent to which ME children were at risk of multiple domain impairments raises concerns about the societal and public health impacts of increasing rates of opioid use amongst pregnant women. By age 4.5 years, 4 out of 5 children born to an opioid-dependent mother had significant developmental concerns in at least one domain, with two-thirds of these children being affected by multiple (≥ 2) or comorbid domain impairments. This rate is very similar to those seen in samples of very preterm born children,4, 22 which in turn has been shown to be highly prognostic of later educational delay.4 These results suggest that, even in this cohort of children whose mothers received good antenatal care and state-funded drug treatment during pregnancy, many were at significant early developmental risk and therefore had a high probability of educational delay by middle childhood. Analysis of impacts on other aspects of functioning is clearly merited, particularly with respect to mental health, social functioning and early onset drug use.

Understanding the factors associated with poor school readiness is crucial for addressing these children’s needs at an early age so as to reduce child and family stress, and even more importantly, lessen public health and social impacts. In this study, a greater level of prenatal substance exposure, male sex, higher levels of maternal social risk and early exposure to an adverse home environment were significant independent predictors of school readiness impairment. This suggests that both biological and socio-contextual factors contributed to children’s later health and neurodevelopmental risks, and in turn overall developmental readiness for school by school entry age. These results are consistent with a large body of child developmental research linking both pre and postnatal factors with a range of adverse child outcomes during early and middle childhood.7, 27-29 Our data confirm the importance of these factors in predicting children’s readiness for school across multiple developmental domains, including their physical well-being and visual-motor development, social-emotional skills, approaches to learning, language development, and cognition and general knowledge.

In particular, we found that increasing maternal substance use during pregnancy was associated with poorer school readiness in this study. This is consistent with previous studies showing that children whose mothers used a greater number of substances including methadone/opioids, cocaine, tobacco, alcohol and cannabis during pregnancy, and whose mothers were heavier substance users during pregnancy, were at risk of behavioural dysregulation, and poorer language and cognitive development.7, 27 Our data suggest that a greater number and quantity of different prenatal substance exposures were associated with increased risk for lower overall school readiness. This may reflect a greater degree of stress experienced by the developing fetus and potentially the early impacts on brain development during gestation. In turn, this early biological vulnerability could have increased their risk for poorer long-term neurodevelopmental outcomes.2

Maternal social risk was another important factor associated with children’s higher rates of school readiness impairment. Individually, maternal social background risks such as early motherhood, low educational attainment, low SES/poverty, single parenthood, and being of ethnic minority have been associated with children’s increased early learning and later educational risk. Our findings are consistent with earlier results from the large-scale Early Childhood Longitudinal Study, which found that children whose mothers have a greater number of these risks tend to have the poorest school entry health and fine motor skills, social-emotional skills, approaches to learning and cognitive outcomes.28

The finding that boys were more likely to have a greater number of school readiness impairments than girls supports existing data that male children may be more vulnerable to inattention, hyperactivity and disruptive behaviour, as well as early language and cognitive difficulties.28 In addition to expected sex differences, it is possible that boys are particularly vulnerability to early developmental disturbance following prenatal opioid and other drug exposures. Nonetheless, it is important to note that whilst ME exposed boys’ neurodevelopmental problems may be apparent from an early age, girls’ early difficulties may be more subtle, and may increase over time with the influence of exposure to compounding environmental risks. It will also be important to keep in mind the impact of the added challenges associated with transitioning from the pre-school or home setting to the more academically and behaviourally demanding formal education setting for the psychosocial development of both boys and girls from this high-risk group.

Even more importantly, we also found that the quality of the postnatal caregiving environment, as assessed using the HOME inventory, was an important predictor of children’s school readiness. This is in line with previous research showing that early HOME scores, reflecting less stimulating and less supportive caregiving environments, were negatively associated with pre-school and later social-emotional and cognitive outcomes.27, 29, 30 We found that the early caregiving environments in which opioid-dependent women were typically raising their children were less well-resourced materially and socially compared to parents in the general population, with exposure to these adverse circumstances serving to independently predict children’s subsequent health and neurodevelopmental outcomes, and in turn the extent of their readiness for school.

Finally, several measurement issues should be acknowledged. First, inspection of our descriptive data revealed considerable variability in impairment/risk rates relative to published test norms, with some measures underestimating impairment (e.g., WPPSI-R), and others aligning closely with test norms (e.g., CELF-P). Thus, the approach we adopted was to determine impairment/school readiness risk on each of our standardized outcome measures based on the score distribution of our regionally representative control group of non-ME children. In general, this approach resulted in a more conservative estimate of the extent of delay/impairment in each of the domains, with fewer ME children being classified as being subject to multiple school readiness impairments than had international standardized test cut-points been used (48% vs. 58%). We would also note that ME children’s risk for school readiness impairment may have been further underestimated due to the exclusion of participants at the outset of the study who were born very preterm, with HIV, and/or fetal alcohol syndrome, which are associated with prenatal methadone exposure and may be risk factors characterizing the more severely affected children of opioid-dependent mothers.

In addition, rather than examining predictors of individual domain impairments, we focused on overall school readiness which may have obscured specific prenatal substance effects. Thus, research examining in finer detail the risk factors and consequences of specific neurodevelopmental outcomes will be important for future studies. Assessment of possible mediators of associations between prenatal substance exposure and these individual school readiness outcomes (e.g., parenting, family instability, maternal well-being) may further aide our understanding of the processes that place these children at risk, and help identify preventative and interventional strategies to support these children and families.

In sum, these findings raise concerns about the preparedness of many methadone- and other substance-exposed children to cope with the physical, social and cognitive challenges of the classroom. They also suggest that problems emerge early and at a rate that justifies developmental monitoring from birth so that difficulties are identified and addressed proactively prior to school entry. Careful assessment of these children’s ongoing strengths and challenges, as well as consideration of possible modifiable factors that may be targeted to improve outcomes, is needed to develop effective strategies to support these children and families, and minimize social, health and educational service impacts from this growing population of infants and children.

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**FIGURE LEGENDS**

**Figure 1.** Study design. Page 6

**SUPPLEMENTAL DIGITAL CONTENT**

**Supplemental Digital Content 1.** Supplemental Table 1. doc