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# Verbal and nonverbal memory in school-aged children born to opioid-dependent mothers

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ABSTRACT

*Background:* The potential long-term developmental effects of prenatal methadone and buprenorphine exposure during pregnancy are still largely unknown.
*Aims:* We investigated memory function in school-aged children of women enrolled in opioid maintenance therapy (OMT) during pregnancy.
*Study design:* Prospective longitudinal cohort study.
*Subjects:* Participants included 41 children (aged 9–11 years), 20 of which had histories of prenatal methadone or buprenorphine exposure.
*Outcome measures:* Verbal and non-verbal memory function was assessed using four subtests from the Test of Memory and Learning - Second edition (TOMAL-2).
*Results:* The OMT group scored lower on both the two non-verbal as well as the two verbal memory tasks, all p-values <.05. Group differences remained for three out of the four subtests after controlling for general IQ. Including maternal tobacco use during pregnancy increased the explanatory power of the model, $R^2$ change of 0.07, p = .04.
*Conclusions:* Children prenatally exposed to methadone or buprenorphine had significantly lower memory performance, however, this association may in part be explained by maternal tobacco use during pregnancy. Consequently, smoking cessation programs should be systematically integrated into opioid maintenance therapy programs for pregnant women.

## 1. Introduction

Opioid use disorder during pregnancy is a major public health issue due to its potential effect on maternal mental and physical health as well as child development. Currently, opioid maintenance therapy (OMT) with long-acting synthetic opioids such as methadone or buprenorphine is recommended to pregnant opioid-dependent women in order to prevent illicit drug use and improve health outcomes. Although neonatal outcomes have been described frequently, potential long-term effects are still largely unknown [1,2].

Recent animal studies suggest that methadone and buprenorphine exposure may specifically affect memory by inducing oxidative stress and inflammation in the hippocampus and decreasing hippocampal brain derived neurotrophic factor (BDNF) protein levels [3]. Behavioral studies with rats have found that prenatal exposure to methadone and buprenorphine can cause memory impairment, particularly on measures of recognition memory and nonspatial memory [4,5]. Although, to our awareness, no studies have specifically studied memory function in children prenatally exposed to methadone or buprenorphine, reduced sustained attention has been observed in children prenatally exposed to methadone [6].

Around 97 % of all pregnant opioid agonist-maintained women smoke during pregnancy [7]. Nicotine binds to acetylcholine receptors that can trigger neural events that are normally ascribed to acetylcholine, including neural cell proliferation, migration, differentiation, apoptosis and synaptogenesis, potentially interfering with normal brain development [8]. Studies have suggested that prenatal exposure to tobacco may cause attentional deficits, behavioral problems, as well as impaired memory function [9]. Children born to opioid-maintained women may therefore be potentially at double risk for negative

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developmental outcomes from both prenatal opioid and nicotine exposure.

The main aim of the present study was to investigate memory function in school-aged children of women enrolled in OMT during pregnancy. Specifically, we assessed 1) whether there is a difference in verbal and non-verbal memory functioning between children of women in OMT and nondrug-exposed comparison children, and 2) the extent to which differences between the OMT and comparison group reflect direct effects of prenatal methadone/buprenorphine exposure or are attributable to other factors related to maternal OMT, including maternal tobacco use during pregnancy.

## 2. Material and methods

### 2.1. Study design and participants

The current study is part of a prospective longitudinal project [10]. Participants in the OMT group were recruited during pregnancy through regional OMT centers and treatment facilities throughout Norway. All women started in an OMT program before conception and used prescribed opioids throughout their pregnancy. The mothers in the comparison group were recruited through local health care centers in and around the city of Oslo and selected based on corresponding due dates. Although an attempt was made at the beginning of the project, it was difficult to recruit families in the control group that matched the OMT group on socio-demographic characteristics. The comparison group therefore consisted mainly of families with a mid-to-high socioeconomic status (SES). The final sample for the ten-year follow-up included 20 children of women in OMT and 21 control children, aged 9–11 years. Demographic, birth, and substance use characteristics are depicted in Table 1.

**Table 1**
Demographic, birth, and substance use characteristics of the OMT and comparison group.

| | OMT ($n = 20$) | Comparison ($n = 21$) | $F/X^2$ | p | $\eta^2/\varphi$ |
|---|---|---|---|---|---|
| *Child characteristics* | | | | | |
| Female sex, *n* (%) | 10 (50.0) | 13 (61.9) | 0.59 | 0.440 | 0.120 |
| Age, years* | 10.9 (0.6) | 10.6 (0.4) | 4.92 | .030 | 0.110 |
| Birth weight, g* | 3108 (728) | 3549 (384) | 5.97 | .020 | 0.130 |
| Birth length, cm** | 47.6 (3.7) | 50.5 (1.4) | 11.4 | .0020 | 0.230 |
| Gestational age, weeks* | 39.0 (3.3) | 40.0 (1.0) | 1.93 | .170 | 0.050 |
| Living with biological parent(s), *n* (%)** | 13 (65.0) | 21 (100) | 8.86 | .003 | 0.470 |
| Treated for NAS, *n* (%) | 14 (70.0) | – | | | |
| *WASI* | | | | | |
| Full Scale IQ*** | 89.75 (10.24) | 105.00 (11.75) | 16.72 | <0.0010 | 0.310 |
| *Mother/fostermother characteristics* | | | | | |
| Higher education, n (%)** | 11 (55.0) | 20 (95.2) | 8.99 | .0030 | 0.470 |
| Employed, *n* (%)** | 13 (65.0) | 21 (100.0) | 8.86 | .0030 | 0.470 |
| Yearly income < 37,000 euro, *n* (%)** | 8 (40.0) | 0 (0) | 10.44 | .0010 | 0.510 |
| Single parenthood, *n* (%)** | 11 (55.0) | 2 (9.5) | 87.55 | .006 | 0.43 |
| *Maternal substance use during pregnancy* | | | | | |
| Tobacco, *n* (%) | 19 (95.0) | 0 | – | – | – |
| Cigarettes, average per day | 11.5 (6.4) | 0 | – | – | – |
| Alcohol, *n* (%) | 2 (10.0) | 0 | – | – | – |
| Marijuana, *n* (%) | 2 (10.0) | 0 | – | – | – |
| Amphetamine, *n* (%) | 6 (30.0) | 0 | – | – | – |
| Benzodiazepine, *n* (%) | 7 (35.0) | 0 | – | – | – |
| Opioids (other than meth/bup), *n* (%) | 5 (25.0) | 0 | – | – | – |
| Methadone, *n* (%) | 12 (60.0) | 0 | – | – | – |
| Buprenorphine, *n* (%) | 8 (40.01) | 0 | – | – | – |
| Meth dose at delivery, mg, mean (range)[a] | 101.8 (10–260) | 0 | – | – | – |
| Bup dose at delivery, mg, mean (range) | 13.5 (3–24) | 0 | – | – | – |

OMT = Opioid Maintenance Therapy; Meth = methadone; Bup = buprenorphine.
Values are given as mean (standard deviation) unless otherwise specified.
[a] One outlier (660 mg methadone) was not included in this mean.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

### 2.2. Procedure

Written informed consent was obtained from the primary caregiver prior to participation and verbal consent was obtained from all participating children. Children were tested individually in a quiet testing room during one session by a trained research assistant blinded to group status of the participants. All children received a gift card worth approximately $10 for their participation at the end of the session. The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki (1964).

### 2.3. Measures

#### 2.3.1. Demographic information

Background data were collected from personal interviews and hospital medical records. The European Addiction Severity Index questionnaire (EuropASI) was administered to all participants in the last trimester in order to measure substance use during pregnancy. In addition, data on pregnancy issues and birth outcomes, including tobacco use, was collected in the last trimester and 3 months after delivery [9]. Self-reported use of substances used was compared to the urine analyses from OMT centers during the last month of pregnancy. There was agreement in all but 1 case, and a mean number of 1.2 samples were collected per week [9].

#### 2.3.2. Wechsler Abbreviated Scale of Intelligence (WASI; [11])

General cognitive ability was assessed using the neuropsychological test battery WASI. WASI contains four subtests (vocabulary, similarities, block design, and matrix reasoning) and provides an age-adjusted IQ-score, a verbal IQ score and a performance IQ score with a mean score of 100 and a standard deviation of 15. The present study used the global IQ score to control for general intellectual ability.

#### 2.3.3. Test of Memory and Learning – Second Edition (TOMAL-2; [12])

Memory functioning was assessed using four subtests of TOMAL-2; an age-normed memory test designed for individuals between the ages of 5–60 years. To measure non-verbal memory, the subtests Facial Memory and Abstract Visual Memory were used, while verbal memory was assessed using the subtests Word Selective Reminding and Paired Recall. Raw scores were converted into scaled scores with a mean of 10 and a standard deviation of 3. In addition, a total memory score was calculated by combining the scores of the four memory tests.

### 2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 26 (SPSS Inc., Chicago, IL, USA). Demographic characteristics were analyzed using a one-way analysis of variance (ANOVA) or chi-square

test where appropriate. The main analysis was divided into three steps. In the first step, between-group differences in memory performance was tested using a one-way between-groups multivariate analysis of variance (MANOVA). Second, multivariate linear regression modelling was used to examine whether any observed between-group differences in memory could be reflective of overall differences in general cognitive abilities. Third, the effects of other confounding factors related to maternal enrolment in OMT were examined in the regression model. Potential confounding factors were selected based on earlier published findings as well as those factors that differed between the OMT and comparison group as described in Table 1. Factors investigated were birth weight, gestational age, maternal education, maternal income, maternal employment, and cigarette, alcohol, benzodiazepine and illegal opioid use during pregnancy. Factors were retained in the model if they were significant at $p < .05$. Preliminary analysis revealed no significant main effects or interaction effects involving gender, living arrangements (biological parents versus foster parents), or type of opioid exposure (methadone versus buprenorphine). Data was therefore collapsed across these variables. In all analyses the statistical significance (α-level) was set at a $p < .05$, two-tailed.

## 3. Results

### 3.1. Memory performance

Table 2 describes the performance of the OMT and comparison group on the memory tasks. A statistically significant difference in memory performance was found between the OMT and comparison group, $F(4,36) = 5.37$, $p = .002$, $\eta 2 = 0.37$. The OMT group scored lower on both the two non-verbal as well as the two verbal memory tasks, all *p*-values $< .05$. The relationship between prenatal methadone/buprenorphine exposure and children's memory performance remained significant after controlling for general IQ, all p-values $< .05$, except for Abstract Visual Memory, which no longer was associated with group status after controlling for general IQ, $p = .14$.

### 3.2. Influence of covariates on memory performance

To investigate the influence of covariates on memory performance, three different models were tested using stepwise multiple regression analysis. The first model, an unadjusted model, investigated only the effects of OMT exposure during pregnancy. The second model adjusted for tobacco use during pregnancy, while the third model adjusted for tobacco use, birth weight, and maternal education and income. Results showed that the unadjusted model accounted for a significant amount of the overall variance in memory performance, $F(1, 39) = 21.27$, $p < .001$, $R^2 = 0.35$. The second model, which included tobacco use, accounted for 42 % of the observed variance, $F(1, 39) = 13.98$, $p < .001$, $R^2 = 0.42$ and resulted in a significant $R^2$ change of 0.07, $p = .04$. The third model accounted for 44 % of the observed variance, $F(1, 39) = 5.46$, $p = .001$, $R^2 = 0.44$, however did not lead to a significant increase in the explanatory power of the model to predict memory performance, $R^2$ change = 0.01, $p = .83$. In the final model, out of all the variable included, only tobacco use during pregnancy added statistically significantly to the prediction ($p = .033$). OMT exposure during pregnancy, birth weight, maternal education, and maternal income did not add additional predictive value, all $p > .05$.

**Table 2**
Unit change in TOMAL-2 memory scale scores among the OMT group ($n = 20$) compared to the comparison group ($n = 21$) at age 10 years.

| | Model 1 (unadjusted) | | Model 2 (cigarette exposure) | | Model 3 (exposure and SES) | |
|---|---|---|---|---|---|---|
| | B | 95% CI | B | 95% CI | B | 95% CI |
| *TOMAL-2* | | | | | | |
| Facial Memory | 2.07* | 0.04, 4.09 | 0.82 | −1.81, 3.45 | 0.77 | −2.02, 3.56 |
| Abstract Visual Memory | 1,90 | −0.65, 4.450 | −0.09 | −3.34, 3.17 | −3.2 | −3.58, 2.95 |
| Word Selective Reminding | 2.45* | 0.46, 4.440 | 2.08 | −0.58, 4.74 | 2.08 | −0.72, 4.87 |
| Paired Recall | 1.87* | 0.15, 3.59 | 1.14 | −1.13, 3.40 | 1.72 | −0.53, 3.98 |

All models, including the unadjusted model, control for full scale IQ from the WASI. Model 2 additionally included prenatal cigarette exposure, and Model 3 additionally included prenatal cigarette exposure, birthweight, maternal income, and maternal education.
* $p < .05$.

## 4. Discussion

To our knowledge, this is the first study to examine verbal and non-verbal memory functioning in school-aged children born to women who used methadone or buprenorphine during pregnancy. Results showed that children born to women in OMT performed lower on both verbal and non-verbal memory tasks. Except for the abstract visual memory task, decreased memory performance could not be explained by differences in general intelligence. These results suggest that children prenatally exposed to methadone or buprenorphine and maternal tobacco use may be at particular risk for memory impairments.

These results support the findings of previous studies. For instance, Wahlsten and Sarman [13] found memory impairments in preschool children born to women in OMT. However, this study did not use a control group and approximately half of the pregnant women enrolled in the study had relapses. Another study administered a working memory-selective attention task to 11 children aged 10–14 year who had been prenatally exposed to methadone or heroin. Compared to non-exposed controls, the opioid-exposed group showed impaired task performance [14]. Potentially, this is caused due the effects of opioids on neuronal aptosis in the hippocampus, although this has only been confirmed in animal studies so far [15]. Additionaly, early childhood adversity, including pre- and postnatal stress may also negatively impact memory development [16].

Although the current study found lower memory task performance in children of women in OMT compared to non-exposed controls, this might not reflect a direct effect of prenatal methadone or buprenorphine exposure. 95 % Of all the women in the OMT group smoked during pregnancy. On average, the opioid-maintained mothers smoked 11 cigarettes a day during pregnancy. When potential risk factors associated with maternal OMT were investigated, it was found that including maternal tobacco use during pregnancy in the model increased the explanatory power significantly. These results are consisted with previous studies that have found a link between maternal tobacco use and reduced cognitive performance in children [17]. Consequently, the reduced memory performance found may be attributable to maternal tobacco use or a combination of prenatal exposure to tobacco and opioids.

Several limitations of this study are worth noting. First, the study had a small sample size due to the limited number of opioid-exposed children that are born in Norway each year, which is a common problem in studies with long-term follow up. Results of this exploratory study should therefore be followed-up by larger scale studies. Second, even though the study tried to investigate the effects of several confounders, other confounding factors including genetic factors and the child's postnatal environmental could also have impacted results. Since the control OMT and control group differed on various other factors besides prenatal methadone or buprenorphine exposure, including socioeconomic status and prenatal exposure to other drugs, these factors may have also influenced results. Strengths of this study included the long-term follow-up period and the novel assessment of memory function. More studies with bigger sample sizes focusing on the long-term development of specific cognitive functions, including memory and

executive function, are required to validate the present findings.

To conclude, the current study found an association between maternal OMT during pregnancy and children's verbal and nonverbal memory skills. However, this association appears to be largely attributable to maternal tobacco use during pregnancy and differences in socioeconomic status. Since memory plays an essential role in learning and the acquisition of new skills, children prenatally exposed to methadone or buprenorphine should be offered regular assessment of their cognitive function. Additionally, smoking cessation programs should be systematically integrated into OMT programs for pregnant women.

## Author disclosures

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## CRediT authorship contribution statement

Konijnenberg was involved in the conception and design of the study, the acquisition of data, analysis and interpretation of data and drafting of the manuscript. Melinder was involved in the conception and design of the study, analysis and interpretation of data, and revising the paper critically for intellectual content.

## Declaration of competing interest

No conflicts to declare.

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