Cognitive and Social-emotional Functioning at 4 ½ Years in Children Born to Mothers who have Received Treatment for Substance Abuse Problems while Pregnant

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My coauthors and I do not have any vested interests that might influence the research. APA ethical standards were followed and The Norwegian Regional Committee for Medical Ethics approved the study. All caregivers gave informed consent for participation in the study. The Norwegian Research Counsel funded the research project.

Abstract

Cognitive and social-emotional functioning at 4 ½ years of age were examined in children born to mothers with substance abuse problems (n=22) recruited from residential treatment institutions while pregnant, and compared to children born to mothers with mental health problems (n=18) and children from a low-risk group (n=26). No significant group differences in cognitive functioning were found, but the children born to mothers with substance abuse problems showed more caregiver-reported social-emotional problems than the low-risk children, like the children born to mothers with mental health problems. Birth weight had an effect on internalizing problems at 4 ½ years and mediated the relation between group and social-emotional problems, though not when controlling for caregiver education, single parenthood and anxiety and depression. At 4 ½ years, seven children born to mothers with substance abuse problems were foster placed. These children had lower birthweight and higher caregiver-rated internalizing problems. In addition to emphasizing the importance of the quality of the prenatal environment, this study suggests that families with previous substance abuse are in need of long term follow-up in order to address social-emotional problems and enhance further positive child cognitive development. The foster placed children may be in particular need of long-term follow-up.

Keywords

Maternal substance abuse; residential treatment; birth weight; cognitive functioning; social-emotional functioning

Introduction

It is well documented that prenatal exposure to opioids and other substances increases the likelihood of lower birth weight, gestational age and head circumference and may lead to Neonatal Abstinence Syndrome (Creanga et al., 2012; Moe, 2002; Moe & Slinning, 2001; Quesada et al., 2012). Furthermore, infants prenatally exposed to substances may have an increased risk of both short- and long-term neurodevelopmental difficulties as expressed through problems with attention and executive functions as well as problems with emotional regulation and behavior (Hans & Jeremy, 2001; Konijnenberg & Melinder, 2013; Moe, 2002; Slinning, 2004).

However, it is difficult to disentangle the effects of prenatal substance exposure from other prenatal and postnatal risk factors. Maternal substance abuse problems often co-exist with other problems such as single parenthood, unstable living conditions, under- and malnutrition, cigarette smoking, lower education and comorbid psychopathology. All these factors may influence the fetus' development and the child's postnatal caregiving environment (Espinosa, Beckwith, Howard, Tyler, & Swanson, 2001; Haller, Knisely, Dawson, & Schnoll, 1993; Hans, Bernstein, & Henson, 1999; Luthar, Cushing, Merikangas, & Rounsaville, 1998; Pajulo et al., 2011; Verheul, 2001). Negative childhood experiences, current lifestyle and psychological problems may compromise caregiving abilities, and potentially influence the child's development in a negative direction independent of or in addition to prenatal substance exposure.

Mothers with ongoing or previous substance abuse problems often act less sensitively and may display more harshness and intrusiveness in social interaction with their infants (Eiden, Schuetze, Colder, & Veira, 2011; Haabrekke, Siqveland, et al., 2014; Pajulo et al., 2011; Pajulo et al., 2001; Siqveland, Smith, & Moe, 2012). Combined with maternal background factors such

as aversive relational experience and distress, the potential biological vulnerability of the infant due to prenatal substance exposure, in addition to further difficulties in self-regulation, may contribute to negative patterns of mother-infant interaction (Eiden, Schuetze, & Coles, 2011; Siqveland, Olafsen, & Moe, 2013; Siqveland et al., 2012). Negativity in mother-infant interaction may further contribute to problems in the child's later social-emotional functioning (Eiden, Schuetze, Veira, et al., 2011), as well as child language skills (Haabrekke, Siqveland, et al., 2014).

Findings of a mutual influence of child and caregiver factors over time can be understood through the transactional model of development (Sameroff & Chandler, 1975; Sameroff & Emde, 1989). Within a transactional framework of understanding these processes, clinical interventions and treatment for families with substance abuse problems should include the overall burden of risk factors rather focus on single risks.

In Norway, there are several inpatient clinics specializing in medically supervised detoxification in a residential setting. In these residential clinics, pregnant women with untreated substance dependence obtain medical and psychological support in becoming drug-free during pregnancy. Pregnant women with a previous history of substance abuse who fear a relapse can also receive help in the clinics.

We have recently reported that infants born to women with poly-substance abuse problems who underwent detoxification in a residential setting during pregnancy have better birth outcomes, such as a higher head circumference and gestational age, as compared to infants born to mothers who received no such treatment (Haabrekke, Slinning, Walhovd, Wentzel-Larsen, & Moe, 2014). In addition, none of the infants born to mothers detoxified during pregnancy had symptoms of Neonatal Abstinence Syndrome. For a subgroup of these children,

neuroanatomical morphometric properties have also been investigated by Magnetic Resonance Imaging (MRI). It was shown that their neuroanatomical features and general ability level did not deviate significantly from that of a subgroup of controls (Walhovd et al., 2015). However, there is little knowledge of the further cognitive and social-emotional development of the children born to mothers who have received treatment for their substance abuse problems relative to groups of children born to mothers with mental health problems and controls.

The infants born to women with poly-substance abuse problems who underwent detoxification in a residential setting during pregnancy had a more advantageous perinatal outcome overall when compared to the group of infants who experienced substance exposure throughout fetal life. However, the birth weight was still significantly lower than that of the comparison infants born to mothers with no substance abuse problems (Haabrekke, Slinning, Walhovd, Wentzel-Larsen, & Moe, 2014). Lower birth weight and low gestational age have been associated with a variety of adverse prenatal environmental conditions. These include maternal substance abuse, cigarette smoking and under- or malnutrition, as well as maternal psychological stress and problems such as anxiety and depression (England et al., 2001; Glover, 2014; Hedegaard, Henriksen, Sabroe, & Secher, 1993; Moe & Slinning, 2001; Secker-Walker, Vacek, Flynn, & Mead, 1998). Furthermore, lower birth weight and gestational age have been found to predict poor cognitive and social-emotional functioning in childhood (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Hediger, Overpeck, Ruan, & Troendle, 2002; Monk, Spicer, & Champagne, 2012; Shah, Robbins, Coelho, & Poehlmann, 2013).

The present study forms part of a longitudinal investigation of the development of children born to mothers with substance abuse problems who have received help for their problems while pregnant. Because substance abuse and mental health problems often co-exist

and are confounded in substance-abuse research, the study includes two concurrent comparison groups. One group included children born to mothers with mental health problems, but not substance abuse problems (high-risk comparison group), and one group included children born to mothers with neither mental health nor substance abuse problems (low-risk comparison group).

The aim of the present study was first to investigate whether children of mothers who had received help for their substance dependence problems differed in cognitive and social-emotional functioning at 4 ½ years of age from the children in the high-risk comparison group, as well as the children in the low-risk comparison group. Due to maternal detoxification and low degree of substance exposure in pregnancy, one would assume more optimized prenatal conditions compared to other populations with continuous prenatal substance exposure, although other adverse prenatal conditions such as cigarette smoking and maternal psychological stress may still be present. Secondly, we were interested in investigating whether differential birth weight could partially mediate possible group differences in both cognitive and social-emotional functioning observed at 4 ½ years. We also expected higher rates of maternal psychiatric symptoms in both the group with substance abuse problems and the high-risk comparison group relative to the low-risk comparison group.

The following research questions were posed:

1. To what extent will the children born to mothers who received help for their substance dependence problems differ in cognitive and social-emotional functioning at 4 ½ years of age, as compared to children of mothers with mental health problems and children of mothers with no such problems?

2. Can birth weight mediate the possible group differences in cognitive and social-emotional functioning at 4 ½ years, also when adjusting for caregiver characteristics such as single parenthood, low education and mental health problems?

Methods

Participants

The participants consisted of 65 mothers and their 66 infants born between 2004-2009. Approval of the study was granted by the Norwegian Regional Committee for Medical Ethics, and all parents and caregivers gave their informed consent. The present study is part of a larger longitudinal follow-up that originally included 83 women recruited during pregnancy (Siqveland et al., 2012).

The present study includes three groups of children and their mothers who were enrolled during pregnancy, with the single inclusion criterion being participation at the 4½-year follow-up assessment. The first group of mothers (*n*=21, 22 children) was recruited from five different residential institutions where they were under treatment for substance abuse problems. Six (28.5%) of these women reported not having used substances while being pregnant but were in residential treatment for the reason of previous history of substance abuse and fear of relapse. For a further specification of substance use within the groups, see Table 1. All the women abusing substances while pregnant were detoxified as part of the residential treatment, though at various points in time depending on when they were admitted to the institutions. When treating a pregnant woman with substance dependence, her individual state and situation are taken into careful consideration. As a result, the exact treatment in terms of medication, therapeutic intervention and other support will vary. What is common to all the institutions that provide help for these women is a close monitoring, as well as a supportive environment. While staying in residential care, the mothers and in some cases their partners live together in an environment with other families. They receive help and guidance from professional therapists regarding nutrition, housekeeping and economy, in addition to mother-infant interaction and psychological

treatment. Seventeen of the 21 women were drug-free by their 3rd trimester, and all were detoxified before the end of their pregnancies. None of the children in this group were born with Neonatal Abstinence Syndrome (NAS[1]). There were no teen-pregnancies. At the 4½-year follow-up, seven (31.8%) of the children born to mothers with substance abuse problems had been foster placed. One child was placed right after birth, one before three months, one between three and 12 months, two between 12 months and 2 years and two between 2 and 4 ½ years. These seven children participated together with their foster parents.

Insert Table 1 approximately here

The second group of mothers (*n*=18) served as a comparison group and was recruited from an outpatient clinic in Oslo where they received psychological treatment in an effort to prevent potential difficulties in the interaction with the child due to their mental health problems, usually depression or anxiety. No use of illicit substances was reported among the women in the second group, but four women reported some binge drinking during the 1st trimester.

The third group of mothers (*n*=26) served as a non-clinical comparison group recruited from well-baby clinics in Oslo. These are free-of-charge clinics where almost all expectant mothers attend for regular follow-ups during pregnancy, and where the parents come with their children from infancy to age 4 for regular health and developmental check-ups and vaccinations. No use of illicit substances was reported among the women in this group, but six women reported some binge drinking during the 1st trimester.

[1] NAS is a constellation of signs and symptoms indicating an irritability of the autonomic nervous system and dysfunctions in the gastrointestinal tract and respiratory system of the infant. Newborns born with NAS are in need of long, often medically complex and costly hospitalizations (Jones et al., 2005; Kaltenbach, Berghella, & Finnegan, 1998).

With the exception of two fraternal twins in the group of mothers with substance abuse problems, all were singleton pregnancies. Hence, a total of 65 caregivers/mothers and 66 children (34 boys) participated in the study. All the children who participated in the study attended preschool.

Procedures

Data for this study were collected at three different time points, in the 3rd trimester during pregnancy, at birth and again at age 4 ½ years. The mothers were interviewed during pregnancy in order to obtain information about their demographic background, somatic and mental health, alcohol consumption and the use of medication and illegal substances. At 4 ½ years, the children's social-emotional and cognitive functioning were assessed. Mother/caregiver symptoms of anxiety and depression were also investigated. A semi-structured interview designed for this study was performed to register the caregivers' education, whether they were living alone or with a partner or other adults, as well as their psychological functioning. In addition, the children's living condition (living with their biological parents or foster parents) was recorded. See Figure 1 depicting who consented to participate at the 4 ½-year follow-up and the ones lost to attrition.

Insert Figure 1 approximately here

Measures during pregnancy and at birth

All mothers were interviewed during pregnancy using the *European Addiction Severity Index* questionnaire (EuropASI), fifth edition (McLellan et al., 1992). The EuropASI consists of

numerous questions related to different areas of functioning. The questions used in the present study covered the use of alcohol, illegal drugs and medication. The reliability and validity of this instrument have been reported to be satisfactory (Carise, McLellan, Gifford, & Kleber, 1999; Kokkevi, Stefanis, Anastasopoulou, & Kostogianni, 1998; McLellan et al., 1992). EuropASI was translated into Norwegian and then back translated (Lauritzen & Nøklebye, 2010); the back translation was accepted by the Amsterdam Institute for Addiction Research.

A structured interview was designed for this study and administered together with EuropASI. This questionnaire consisted of items related to the residential treatment during pregnancy, and it also included questions about how frequently illegal substances and nicotine were used, as well as the amount and frequency of alcohol consumption both before and during pregnancy.

Birth weight was obtained from each child's medical record at the hospitals where the mothers gave birth.

Measures at 4 ½ years

Child measures

WPPSI-III

In order to assess key aspects of cognitive functioning the Norwegian edition of Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III) (Wechsler, 2008) was administered. The WPPSI-III is constructed of 14 subtests measuring verbal and logical/problem-solving skills as well as tasks capturing speed and receptive language. The WPPSI-III yields a verbal IQ and a performance IQ as well as sum scores of speed and receptive language, all with expected means of 100 and expected standard deviations of 15 based on

Norwegian norms. The full-scale IQ is calculated based on seven of the subscales and was obtained for all 66 children.

ASEBA

To assess child social-emotional problems two versions of Achenbach System of Empirically Based Assessment (ASEBA) were used; the Child Behavior Check List (CBCL) 1 ½ -5 and the Teachers Report Form (TRF) (Achenbach & Rescorla, 2000). These questionnaires are well-validated, standardized assessment protocols for child social-emotional problems designed for completion by primary caregivers and teachers. Norwegian norms for ASEBA were not available at the time of testing, hence US norms were applied. ASEBA has been translated into Norwegian and then back translated with the permission of T.M. Achenbach[2]. Each mother/caregiver was asked to fill out the form in advance of the examination. Granting mother/caregiver consent, following the 4 ½-year examination the TRF was sent to the child's preschool accompanied by a letter. The preschool teacher with the closest relation to the child was asked to fill out the form and return it by mail.

The CBCL and the TRF consist of 99 items, with each item to be answered on a three-point scale from 0 to 2, in which 0 is "not true," 1 is "somewhat true" and 2 is "often true." The items constitute eight factors of emotional, behavioral and social problems, and the statements can also be categorized into internalized and externalized behaviors, in addition to a total behavior problem score. Internalized behaviors include items from the four dimensions of *emotionally reactive, anxious/depressed, withdrawn* and *somatic complaints*. Externalized behaviors include items from the two dimensions of *attention problems* and *aggressive behavior*.

[2] Translated to Norwegian by T.S. Nøvik and colleagues in 2002. Back translated by S.Schanche and T. Ueland in 2002.

The total behavior problem score also includes the dimension of *sleep problems* (only in the CBCL), as well as the rest of the items described as *other problems*. A T-score from 65 to 69 is considered within the borderline range, and a T-score above 70 is considered within a clinical range of problems. To take account of the full range of variation in the scales, the sum of the raw scores were used in the analyses in the present study (Achenbach & Rescorla, 2000).

Caregiver measures

An assessment of anxiety and depression was obtained by use of the short version of the Hopkins Symptom Checklist, SCL-25 (Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974), which the mother/caregiver was asked to fill out in advance of the 4½-year examination. The SCL-25 is a self-administered questionnaire consisting of 25 items representative of the symptoms of anxiety and depression, in which each item is rated on a five-point scale ranging from 0 (not at all) to 4 (very much). The SCL-25 has proven to have satisfactory validity and reliability as a measure of psychological distress (Strand, Dalgard, Tambs, & Rognerud, 2003). Ten of the items are related to symptoms of anxiety and 15 to symptoms of depression. The total sum score was used in the present study as a measure of presence of symptoms of anxiety and depression. Scale scores were computed as means of valid items multiplied by the total number of items, provided that at least half of the items within each scale were valid. Subsequently, the scale score was transformed into a range from 0 (no symptoms) to 100 (maximum symptoms), while the reliability of the total scale, expressed as Cronbach's alpha, was 0.96.

Demographic characteristics and substance use

A semi-structured interview designed for the purpose of the study was performed to register the caregivers' education, whether they were living alone or with a partner or other adults, as well as psychological functioning and problems with current substance use. The child's living condition (living with biological parents or foster parents) was also recorded. In addition, the mothers/caregivers were asked whether they currently had problems with substance abuse, and whether they were receiving help for substance dependence problems.

Statistical methods

Descriptive statistics was applied to investigate the sample characteristics of substance use during pregnancy. Linear regressions with group as main independent variable and gender as adjustment variables were conducted to test group differences on birth weight and WPPSI-III (in which standardized scores are rated according to age).

Power calculations for this study were based on data already collected for the purpose of a larger longitudinal study (Siqveland et al., 2012). The power calculations investigated what value of the effect size Cohen's f^2 could be detected with 80% power for a sample size n=66, in a 4 degrees of freedom model (with the covariates three-category group and adjustment for gender and age) for cognitive and socioemotional development.

Linear regression analyses with group as main independent variable, and gender and test age as adjustment variables, were conducted to test for group differences in CBCL and TRF raw scores. Furthermore, sensitivity analyses excluding the twins were performed for child birth weight. For WPPSI-III, CBCL,TRF and SCL, sensitivity analyses were performed excluding the foster children/foster mothers, with 95% bootstrap BC_a intervals (10 000 bootstrap replications)

computed for changes when the significance of the change was not clear from considerations of overlap of confidence intervals.

One-way ANOVAs were conducted to test for differences between groups on current symptoms of caregiver anxiety and depression (SCL-25). Exact chi-square tests were conducted to investigate group differences in caregiver education at 4 ½ years and single parenthood. Post-hoc Tukey Honestly Significant Difference (HSD) tests were also performed to examine the differences between pairs of groups in the ANOVA analyses, and in the linear regression analyses with adjustment for gender only. In the linear regression analyses with adjustment for age and gender as well as in the chi-square analyses, it was corrected for multiple testing by use of the Holm procedure (Aickin & Gensler, 1996).

To investigate whether group differences at 4 ½ years of age were mediated by birth weight, mediation analyses were run for the outcome variables (cognitive and social-emotional functioning at 4 ½ years), with birth weight as a possible mediator of group. Moreover, to investigate whether birth weight mediated group differences independently of social risk factors such as single parenthood, low caregiver education and caregiver mental health problems measured at 4 ½ years, mediation analyses were also performed adjusting for these variables. A dichotomous variable capturing a higher/lower caregiver education was computed and used in the analyses.

Mediated effect in linear regression is defined as the product of the two regression coefficients in the mediated path. The mediation analyses were performed by the bootstrap resampling method using 10000 re-samples of the data, and bootstrap bias corrected 95% confidence intervals were computed for the mediated effects. Relationships were considered

significant if 0 was outside these intervals (Hayes, 2013), whereas *p*-values were obtainable for the direct effects only.

Participants and non-participants at the 4 ½-year follow-up were compared on birth weight and maternal age using independent samples T-tests. Maternal education at pregnancy was categorized into *less than high school and no higher education, high school and no higher education,* and *higher education*. Participants and non-participants at the 4 ½-year follow-up were compared on maternal education using an exact chi-square test.

Analyses were performed using a significance level of 5% and were conducted using SPSS 19.0 (IBM Corp., Armonk, NY), with the PROCESS macro (Hayes, 2013) for conditional process analysis, Holm adjustment using the R (The R Foundation for Statistical Computing, Vienna, Austria) function p.adjust, bootstrapping using the R packages boot for bootstrap analyses and MBESS (function ss.power.R2) for power calculations.

Results

Caregiver characteristics

As reported in Table 2, there was no significant difference in caregiver total symptoms of anxiety and depression between the study group and the low-risk group (p=.497). When excluding the foster mothers, the difference increased, and this increase (2.72, CI 0.94 to 7.25) was statistically significant. The group of mothers with mental health problems reported significantly higher levels of symptoms of anxiety and depression relative to the low-risk group (p<.001) and the mothers/caregivers in the study group (p=.001). There was a significantly higher rate of single parenting in the study group than among the high-risk comparison mothers (p=.011) and the low-risk mothers (p=.002), while there was no significant difference between the two latter groups

(p=.953). Chi-square tests yielded a significant difference in caregiver educational level between the study group and the low-risk comparison group (p<.001), but not between the two risk groups (p=.102). None of the mothers in the study group reported current problems with substance abuse, but as three mothers at the 4 ½ years assessment were in Opioid Maintenance Treatment (OMT) at that time, they reported receiving treatment for substance abuse problems. In addition, one of the mothers reported receiving help for recurring thoughts and craving for substances.

Insert Table 2 approximately here

Birth outcomes

As reported in table 2, the children born to mothers with substance abuse problems had significantly lower birth weight than the low-risk comparison children (-447.1, CI -766.5 to -127.6, p=.004), as did the children born to mothers with mental health problems (-459.0, CI -797.2 to -120.9, p=.005). There was no significant difference between the study group and the high-risk comparison group (11.9, CI -338.5 to 364.4, p=.996). There was no significant effect of gender (F = .262, p = .610) on birth weight. In the sensitivity analyses, when excluding the twins, the results were not substantially different. When the analyses were rerun with the foster children excluded, the difference in birth weight between the children born to mothers with substance abuse problems and the comparison children became smaller (-298.5, CI -647.3 to 50.4), and the reduction (-148.6, CI -338.9 to -40.7) was statistically significant.

Group differences in cognitive and social-emotional functioning at 4 ½ years

Power calculations showed that with sample size 66 a value of Cohen's f^2 of 0.20 (corresponding to an R^2=0.17) may be detected with 80% power. This value is close to the boundary 0.15 of medium effect size (Cohen, 1988).

As seen in table 3 in the model of cognitive functioning by group and gender, there were no significant differences between the groups in cognitive functioning, but a trend in this direction was found on the WPPSI-III full-scale (*p*=.096) and performance IQ (*p*=.082). This was primarily due to the relatively lower scores of the children born to mothers with substance abuse problems. There were no significant group differences on any of the other subscales of WPPSI-III. However, there was a significant effect of gender on full-scale (F = 6.165, *p* = .016) and performance IQ (F=7.134, *p*=.010), with boys scoring lower than girls (full-scale: boys: M=95.35, SD=10.4, girls: mean 100.5, SD=8.3, performance IQ: boys: M 94.4, SD=9.9, girls: M=100.2, SD=10.7). When the analyses were run with the foster children excluded, the results of the analyses did not change noteworthy.

In the model of social-emotional functioning by group, gender and age, caregiver-rated total problems were significantly higher in the group of children born to mothers with substance abuse problems than the low-risk comparison children (14.34, CI 2.68 to 25.99, *p*=.017). No significant difference was found between the two risk groups (2.60, CI-11.20 to 16.40, *p*=.708). There was also a significant difference between the low-risk and the high-risk comparison children (16.94, CI 4.35 to 29.53, *p*=.009). Three children (13.6%) born to mothers with substance abuse problems and one child (6.25%) born to mothers with mental health problems scored within the borderline (T-score above 65) or clinical range (T-score above 70) of caregiver-reported total problems. None of the children from the low-risk group scored within

the borderline or clinical range. There was a significantly higher level of caregiver-reported child internalizing problems in the study group as compared to the low-risk children (5.49, CI 1.55 to 9.42, *p*=.007) but not between the two risk groups (0.33, CI-4.33 to 4.99, *p*=.889). Again, the high-risk comparison children were rated higher on internalizing problems than the low-risk comparison children (5.81, CI 1.56 to 10.06, *p*=.008). Three children (13.6%) born to mothers with substance abuse problems and two (12.5%) children born to mothers with mental health problems scored within the borderline or clinical range on caregiver-rated internalizing problems, while none of the children from the low-risk group did. No significant relationships with gender were found on any of these measures. There were trends towards differences in CBCL externalizing behavior between the children born to mothers with substance abuse problems and the low-risk comparison children (4.13, CI -0.06 to 8.32, *p*=.053), and between the high-risk and low-risk comparison children (4.25, CI -0.27 to 8.78, *p*=.065). There was no significant difference between the two risk groups (0.12, CI -4.84 to 5.08, *p*=.961). Two children born to mothers with substance abuse problems (9.1%) and one child born to mothers with mental health problems (6.25%) scored within the borderline or clinical range on caregiver-rated externalizing behavior.

When the analyses were run with the children placed in foster care excluded, the difference for CBCL internalizing problems between the children born to mothers with substance abuse problems and the comparison children became smaller (3.08, CI 0.29 to 5.87, *p*=.031), and the reduction (2.41, CI 0.03 to 6.6) was statistically significant. The difference in CBCL total problems also became smaller (7.12, CI -0.71 to 14.96, *p*=.074), though the reduction (7.22, CI -0.5 to 21.7) was statistically insignificant.

On the preschool teacher-rated reports (TRF) of child social-emotional problems, no significant group differences were found on any of the scales ($p \geq .161$) (Table 3). Two children born to mothers with substance abuse problems (9.5%) and three low-risk children (12.5%) were rated within the borderline or clinical range of total behavior problems by their preschool teachers, while none of the high-risk comparison children were rated within the borderline or clinical range. As for externalizing problems four children born to mothers with substance abuse problems (19%) and three low-risk comparison children (12.5%) were rated within the borderline or clinical range. For internalizing problems two children born to mothers with substance abuse problems (9.5%) and three low-risk comparison children (12.5%) were rated within the borderline or clinical range by their preschool teacher.

Insert Table 3 approximately here

Analyses with birth weight as mediator

The analyses with cognitive skills at 4 ½ years as outcome variables showed no significant effect of birth weight as a mediator. For the WPPSI full-scale IQ the mediated effect was 0.57 (CI -0.81 to 1.75), for Verbal IQ the mediated effect was 0.46 (CI -0.73 to 1.54), for performance IQ the effect was 0.85 (CI -0.63 to 2.39), for Speed it was -0.07 (CI -1.41 to 0.90) and for Receptive language the mediated effect was 0.21 (CI -1.38 to 1.51). Furthermore, birth weight showed no significant direct effect on any of the WPPSI outcome variables ($p \geq .185$).

In the analysis with caregiver-rated child total behavior problems as outcome variable, the effect of group was significantly mediated by birth weight (-2.28, CI -5.29 to -0.05), however the mediated effect was no longer significant when controlling for caregiver education, single

parenthood and present caregiver symptoms of depression and anxiety (-2.69, CI -6.61 to 0.24). Similarly, a significant mediated effect of birth weight on group allocation was found on caregiver-reported child internalizing problems, (-0.94, CI -2.10 to -0.07), but this effect also became insignificant when controlling for caregiver education, single parenthood and caregiver depression and anxiety, (-1.16, CI -2.72 to 0.06). Birth weight showed no significant direct effect on caregiver-reported total problems (p=.111), but a significant direct effect on internalizing problems (-0.38, p= .039). There was also a significant direct effect of caregiver depression and anxiety (0.34, p=.039) on caregiver-reported total problems. There were trends towards effects of caregiver educational level (3.77, p= .061) and caregiver depression and anxiety (0.10, p=.064) on child internalizing problems. No significant mediated effect via birth weight with CBCL externalizing problems as outcome variable was found, (-0.44, CI -1.55 to 0.26), and no significant effect of birth weight (p>.308) on CBCL externalizing problems. With preschool teacher-rated reports (TRF) of social-emotional problems as outcome variables, no significant mediated effect of group via birth weight was found for either internalizing problems (-0.48, CI -1.19 to 0.11), externalizing problems (0.13, CI -0.90 to 1.55) or total problems (-0.48, CI -2.29 to 1.63). Neither were there any significant effects of birth weight on any of the TRF outcome variables (p≥.145).

Attrition analyses

Maternal age during pregnancy did not differ significantly (p= .728) between participants and non-participants at the 4 ½-year follow-up, while participants had a significantly higher birth weight than the non-participants (difference 295g, 95% CI 20 to 570, p= .036). A lower proportion of participants (52.2%) with less than high school education took part in the 4 ½ –

year follow-up, compared to the participants with high school (84.6%) and higher education (86.0%), and this difference was statistically significant (p= .006).

Discussion

The aim of this study was to investigate whether children born to mothers who had received help for their substance dependence problems (study group) differed in cognitive and social-emotional functioning at 4 ½ years of age, as compared to children of mothers with mental health problems (high-risk comparison group) and children of mothers with no such problems (low-risk comparison group). The results showed no significant group differences in cognitive functioning at 4 ½ years. However, regarding social-emotional functioning at 4 ½ years, the children in the study group had significantly more caregiver-rated internalizing problems than the children in the low-risk comparison group, and similar to that of the high-risk comparison group. The children born to mothers with substance abuse problems and the children in the high-risk comparison group also had significantly more total behavioral problems, and a trend towards more caregiver-reported externalizing problems than the low-risk comparison children. Nonetheless, it should be noted that although there were significant group differences, only three children in the study group (13%) scored within the borderline or clinical range.

As a group, the children born to mothers with substance abuse problems on average scored lower on all WPPSI subscales and full-scale IQ than the high-risk comparison group, who in turn scored lower than the low-risk comparison children. However, none of these group differences were statistically significant. The study group in the present sample was characterized by a low level of prenatal substance exposure as the women with ongoing substance abuse were detoxified while pregnant and lived under safe and stable conditions as

well as high monitoring when in residential care. Earlier studies documenting differences in cognitive functioning relative to controls have often been based on samples of children with higher levels of prenatal substance exposure and less supportive follow-up (Hans & Jeremy, 2001; Moe, 2002; Moe & Slinning, 2002). The families where the mothers had substance abuse problems received further help and guidance from the treatment institutions after the children were born. Moreover, through the child protection service, the Norwegian welfare system financially supports disadvantaged families so that the children can attend preschool, which all children in the present study did. Taken together, all these factors may have contributed to and enhanced positive cognitive development. However, it should be mentioned that WPPSI possibly did not capture some of the subtler problems of concentrating and attention span, which are often found among children prenatally exposed to opiates and other substances (Konijnenberg & Melinder, 2013; Lester & Tronick, 1994; Melinder, Konijnenberg, & Sarfi, 2013). Furthermore, it is possible that statistically significant group differences in cognitive functioning at age 4½ years would have been detected given a larger sample size. Non-significant findings should not be given too much weight in small samples; it is therefore important to interpret the lack of group differences in cognitive functioning with caution. Also, the group differences in cognitive functioning, although not statistically significant, may emerge in later childhood with increasing demands in a school setting.

With regard to social-emotional functioning, we found no significant group differences on the teacher-rated problem report (TRF) in either externalizing or internalizing behavior. The finding of significant group differences in caregiver-reported internalizing problems, but not in the reports provided by the preschool teachers, may be due to multiple factors. One possibility is that behavioral problems are more easily observable in the home environment where there are

fewer children, and the parents have more experiences reading their children's subtle cues. It is likely that the preschool teachers overlooked internalizing problems such as anxiousness, depressed mood and withdrawal from play and social interaction. In preschool, "quiet" children may not get much attention from the preschool teachers who have many children to tend to, and they do not pose the same problems in a group of children as those with externalizing behavior. It is also likely that the children's behavior is situation-specific and varies between the preschool and home environment (Achenbach, McConaughy, & Howell, 1987), and that the children showed more problem behavior at home. In addition, the caregivers in the two risk groups may have a readiness to see problem behavior in the children due to their own experiences of psychological stress. It has been found that maternal depression is associated with negative perceptions of children (Gelfand & Teti, 1990); relatedly we found that caregiver anxiety and depression were associated with caregiver report of child total behavior problems. Perceived child behavior may be negatively influenced by anxiety and depression, while at the same time child behavior problems may influence caregiver worries and depressed moods, and these factors may also mutually influence and reinforce each other over time through transactional processes. (Sameroff & Chandler, 1975; Sameroff & Emde, 1989). In the present study, a high incidence of symptoms of anxiety and depression were shown among the high-risk comparison mothers. When including only the biological mothers from the study group, the difference in the report of symptoms of anxiety and depression between the study group and the low-risk comparison group increased, and this increase was statistically significant, suggesting that the biological mothers with a history of substance abuse experienced the highest levels of anxiety and depression in this group.

Among the children born to mothers with substance abuse problems, seven were placed in foster care before the age of 4 ½ years. The foster children showed higher levels of internalizing problems among those who were born to mothers with substance abuse problems. Thus, the difference in caregiver-reported child internalizing behavior problems between the children born to mothers with substance abuse problems and the low-risk comparison children was reduced when the foster children were excluded from the analyses. The children who grew up in foster care had experienced an adverse caregiving environment prior to their placement. Only two of these children were placed in foster care before the age of 3 months, while the other five were placed later and two children as late as 2–4 ½ years. Some of the children may also have moved more than once, as the first placement of foster children in Norway often is in an emergency shelter home where the child stays until a suitable foster home is provided.

Birthweight may also play a part as the foster children had a lower birth weight compared to the other children in the group of children born to mothers with substance abuse problems, which indicates a higher biological vulnerability. The difference in birth weight between the children in the study group and the low-risk comparison children was reduced when the foster children were excluded from the analyses, and this reduction was statistically significant. Lower birth weight can be a marker for a variety of adverse prenatal environmental conditions such as maternal substance abuse, cigarette smoking and under- or malnutrition as well as maternal psychological stress during pregnancy (England et al., 2001; Glover, 2014; Hedegaard et al., 1993; Moe & Slinning, 2001; Secker-Walker et al., 1998). Vulnerability caused by prenatal *and* postnatal risk factors is a plausible explanation for the higher levels of caregiver-reported internalizing problems in the foster children.

Furthermore, we found that birth weight partly mediated group differences in child internalizing problems as well as total problems reported by the caregivers; even so, the mediating effect of birth weight was not significant when we controlled for caregiver socio-demographic risk factors such as single parenthood, lower educational level and present symptoms of anxiety and depression. This illustrates the difficulty in disentangling the individual effects of various risk factors on child social-emotional functioning. Risk factors such as those mentioned above often coexist and may operate in similar ways influencing developmental outcome. Birth weight was also found to have a direct effect on caregiver-reported child internalizing problems. Prenatal factors influencing birth weight could potentially interact with risk factors in the proximal caregiving environment, enhancing the adverse effects over time. Even though the birth weight in the current sample was mostly within the normal range, it is possible that normal variations play a part in further transactional processes.

The children in the study group and the high-risk comparison group were similar in terms of social-emotional functioning measured at 4 ½ years, and birth weight relative to the low-risk comparison group. The mothers who abused substances while pregnant were detoxified, meaning less prenatal substance exposure relative to some other studied populations (i.e. Creanga et al., 2012; Hans & Jeremy, 2001; Moe, 2002; Moe & Slinning, 2001; Quesada et al., 2012). Nevertheless, there are important differences between the study group and the high-risk comparison group that should not be overlooked. As mentioned above, seven of the children born to mothers with substance abuse problems were foster placed before the age of 4 ½ years, which suggests exposure to an adverse caregiving environment prior to their placements. In addition to needing a new caregiver, these children also had to overcome the loss of their primary caregiver from whom they had moved away. Some may also have experienced more

than one placement, which could have led to vulnerability and disruption in the development of attachment. In addition, the children in the study group had, although to various degrees, experiences prenatal substance exposure with potential influence on prenatal development of neurobiological functions. In addition, the mothers in this group were more often single mothers compared to the mothers in the other two groups. The findings of higher levels of social-emotional problems in the study group and the high-risk comparison group may therefore be explained by both prenatal and postnatal conditions, hence possibly affecting the development through different pathways.

Limitations and suggestions for future research

Limitations of the present study include a relatively small sample size, and the results must therefore be interpreted with caution. This applies mainly to the non-significant findings as we cannot rule out possible group differences in cognitive functioning with a larger sample size. Challenges in cognitive functioning may also become more salient with further development and adaptation to more structured settings, such as classroom and school environment. These are factors that should be investigated further. It is also possible that the tests of cognitive functioning used in the this study did not capture subtle problems with concentration and attention span often observed in children prenatally exposed to substances. Also, the fact that there was some alcohol consumption during pregnancy in all three groups as well as binge drinking in the 1st trimester in as much as six mothers in the low-risk comparison group could be a potential third variable influencing the findings, and possibly explain the lack of group differences in cognitive functioning.

It is also important to recognize that the group of children born to mothers with substance dependence problems is a diversified group. Moreover, seven of the children in this group were in foster care but placed at various time points. The children in this subgroup probably experienced a variety of biological and environmental risks, making it difficult to disentangle possible causal mechanisms. At the same time, the heterogeneity of this group reflects a general challenge in studying outcomes among children at risk born to mothers with substance dependence problems.

The test situation was designed to support the child in accomplishing the tasks within a reasonable time limit. The test leaders were not blind to group allocation, and because the study constitute of vulnerable clinical groups extra care was taken to protect the participants and respect their challenging life situation. It was of importance to make the meetings with the participants a positive experience for both the child and caregiver. Although attempting to create equal conditions for every child tested, some children needed more breaks than others in completing the tasks. A systematic registration of the number of breaks needed and other challenges during the test situation could be important aspects that should be addressed in future studies.

There were a few missing preschool reports on child social-emotional problems, as some of the mothers in the study group and in the high-risk comparison group did not want the teachers to fill out questionnaires about their children. The reason mothers gave for this reservation was primarily that they did not wish the teachers to know about their child's background. In a small sample such as the present one, it is possible that these missing preschool reports partly might explain the lack of group differences in teacher reported social-emotional functioning.

It is also important to consider a possible attrition bias when generalizing from the findings. Although there was no significant difference in maternal age between those who remained in the study at the 4 ½-year follow-up and those who did not, we did find that the children's birth weight was significantly higher in those who remained in the study. A significantly larger proportion of mothers with a higher educational level (measured during pregnancy) also remained at the 4 ½ year followed up as compared to those with a lower educational level. It is possible that this has created a bias in the study that could account for the lack of group differences in cognitive functioning.

Clinical implications

The children born to mothers with substance abuse problems who were detoxified in pregnancy experienced less prenatal substance exposure and other non-optimal prenatal conditions related to substance use in pregnancy as compared to other samples. Furthermore, all these families received support from the child protection services, such as financial support and free preschool. The findings suggest that interventions during pregnancy, as well as support after birth, may give these children a better starting point in life. However, the children were rated higher on social-emotional problem behavior by their caregivers, although only 13% were rated within borderline or clinical range. The social-emotional problems were partly related to birth weight, but also to caregiver symptoms of anxiety and depression. The mothers with a history of substance abuse were more often single parents and had a lower educational level, potentially affecting caregiving capacity.

In addition to lending support to the importance of the quality of the prenatal environment, the study demonstrates that these families are in need of long-term follow-up and

support in order to discover and address the children's social-emotional problems, as well as stimulating their cognitive development. Caregivers' mental health is an important precursor for stable and supporting parenting behavior, and interventions should therefore target the caregivers' mental health problems to ensure supportive caregiving. Children placed in foster care, and their new families, may be in need of long-term follow-up, in which interventions should include the entire burden of risk factors.

References

Aarnoudse-Moens, C. S., Weisglas-Kuperus, N., van Goudoever, J. B., & Oosterlaan, J. (2009). Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics, 124*(2), 717-728. doi:10.1542/peds.2008-2816

Achenbach, T. M., McConaughy, S. H., & Howell, C. T. (1987). Child/adolescent behavioral and emotional problems: Implications of cross-informant correlations for situational specificity. *Psychological Bulletin, 101*(2), 213-232. doi:10.1037/0033-2909.101.2.213

Achenbach, T. M., & Rescorla, L. (2000). *Manual for the ASEBA School-Age Forms & Profiles*: Aseba Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Aickin, M., & Gensler, H. (1996). Adjusting for multiple testing when reporting research results: the Bonferroni vs Holm methods. *American Journal of Public Health, 86*(5), 726-728.

Bjornebekk, A., Siqveland, T. S., Haabrekke, K., Moe, V., Slinning, K., Fjell, A. M., & Walhovd, K. B. (2014). Development of children born to mothers with mental health problems: subcortical volumes and cognitive performance at 4(1/2) years. *European Child and Adolescent Psychiatry*. doi:10.1007/s00787-014-0625-9

Carise, D., McLellan, A. T., Gifford, L. S., & Kleber, H. D. (1999). Developing a National Addiction Treatment Information System: An Introduction to the Drug Evaluation Network System. *Journal of Substance Abuse Treatment, 17*(1–2), 67-77. doi:10.1016/S0740-5472(98)00047-6

Cohen J. E. (1988). Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Creanga, A. A., Sabel, J. C., Ko, J. Y., Wasserman, C. R., Shapiro-Mendoza, C. K., Taylor, P., . . . Paulozzi, L. J. (2012). Maternal drug use and its effect on neonates: a population-based study in Washington State. *Obstetrics and Gynecology, 119*(5), 924-933. doi:10.1097/AOG.0b013e31824ea276

Derogatis, L. R., Lipman, R. S., Rickels, K., Uhlenhuth, E., & Covi, L. (1974). The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. *Behavioral Science, 19*(1), 1-15. doi:10.1002/bs.3830190102

Eiden, R. D., Schuetze, P., Colder, C. R., & Veira, Y. (2011). Maternal cocaine use and mother-toddler aggression. *Neurotoxicology and Teratology, 33*(3), 360-369. doi:10.1016/j.ntt.2011.03.001

Eiden, R. D., Schuetze, P., & Coles, C. D. (2011). Maternal cocaine use and mother-infant interactions: Direct and moderated associations. *Neurotoxicology and Teratology, 33*(1), 120-128. doi:10.1016/j.ntt.2010.08.005

Eiden, R. D., Schuetze, P., Veira, Y., Cox, E., Jarrett, T. M., & Johns, J. M. (2011). Cocaine Exposure and Children's Self-Regulation: Indirect Association via Maternal Harshness. *Front Psychiatry, 2*, 31. doi:10.3389/fpsyt.2011.00031

England, L. J., Kendrick, J. S., Wilson, H. G., Merritt, R. K., Gargiullo, P. M., & Zahniser, S. C. (2001). Effects of smoking reduction during pregnancy on the birth weight of term infants. *American Journal of Epidemiology, 154*(8), 694-701.

Espinosa, M., Beckwith, L., Howard, J., Tyler, R., & Swanson, K. (2001). Maternal psychopathology and attachment in toddlers of heavy cocaine-using mothers. *Infant Mental Health Journal, 22*(3), 316-333. doi:10.1002/imhj.1004

Gelfand, D. M., & Teti, D. M. (1990). sThe effects of maternal depression on children. *Clinical Psychology Review, 10*(3), 329-353.

Glover, V. (2014). Maternal depression, anxiety and stress during pregnancy and child outcome; what needs to be done. *Best Practice & Research: Clinical Obstetrics & Gynaecology, 28*(1), 25-35. doi:10.1016/j.bpobgyn.2013.08.017

Haabrekke, K. J., Siqveland, T., Smith, L., Wentzel-Larsen, T., Walhovd, K. B., & Moe, V. (2014). Mother–Child Interaction and Early Language Skills in Children Born to Mothers with Substance Abuse and Psychiatric Problems. *Child Psychiatry and Human Development*, 1-13. doi:10.1007/s10578-014-0512-0

Haabrekke, K. J., Slinning, K., Walhovd, K. B., Wentzel-Larsen, T., & Moe, V. (2014). The perinatal outcome of children born to women with substance dependence detoxified in residential treatment during pregnancy. *Journal of Addictive Diseases, 33*(2), 114-123. doi:10.1080/10550887.2014.909698

Haller, D. L., Knisely, J. S., Dawson, K. S., & Schnoll, S. H. (1993). Perinatal Substance Abusers: Psychological and Social Characteristics. *The Journal of nervous and mental disease, 181*(8), 509-513.

Hans, S. L., Bernstein, V. J., & Henson, L. G. (1999). The role of psychopathology in the parenting of drug-dependent women. *Development and Psychopathology, 11*(4), 957-977. doi:10.1017/S0954579499002400

Hans, S. L., & Jeremy, R. J. (2001). Postneonatal mental and motor development of infants exposed in utero to opioid drugs. *Infant Mental Health Journal, 22*(3), 300-315. doi: 10.1002/imhj.1003

Hayes, A. F. (2013). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. New York, NY: Guilford Press; US.

Hedegaard, M., Henriksen, T. B., Sabroe, S., & Secher, N. J. (1993). Psychological distress in pregnancy and preterm delivery. *BMJ, 307*(6898), 234-239.

Hediger, M. L., Overpeck, M. D., Ruan, W. J., & Troendle, J. F. (2002). Birthweight and gestational age effects on motor and social development. *Paediatric and Perinatal Epidemiology, 16*(1), 33-46.

Jones, H. E., Johnson, R. E., Jasinski, D. R., O'Grady, K. E., Chisholm, C. A., Choo, R. E., . . . Milio, L. (2005). Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug and Alcohol Dependence, 79*(1), 1-10. doi:10.1016/j.drugalcdep.2004.11.013

Kaltenbach, K., Berghella, V., & Finnegan, L. (1998). Opioid dependence during pregnancy. Effects and management. *Obstetrics and Gynecology Clinics of North America, 25*(1), 139-151.

Kokkevi, A., Stefanis, N., Anastasopoulou, E., & Kostogianni, C. (1998). Personality disorders in drug abusers: Prevalence and their association with axis i disorders as predictors of treatment retention. *Addictive Behaviors, 23*(6), 841-853. doi: 10.1016/S0306-4603(98)00071-9

Konijnenberg, C., & Melinder, A. (2013). Neurodevelopmental investigation of the mirror neurone system in children of women receiving opioid maintenance therapy during pregnancy. *Addiction, 108*(1), 154-160. doi:10.1111/j.1360-0443.2012.04006.x

Lauritzen, G., & Nøklebye, H. (2010). *EuropASI Addiction Severity Index, European Adaptation of the 5th American edition*. SIRUS.

Lester, B. M., & Tronick, E. Z. (1994). The effects of prenatal cocaine exposure and child outcome. *Infant Mental Health Journal, 15*(2), 107-120. doi:10.1002/1097-0355(199422)15:2<107::AID-IMHJ2280150203>3.0.CO;2-R

Luthar, S. S., Cushing, G., Merikangas, K. R., & Rounsaville, B. J. (1998). Multiple jeopardy: Risk and protective factors among addicted mothers' offspring. *Development and Psychopathology, 10*(1), 117-136. doi:10.1017/S0954579498001333

McLellan, A. T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., . . . Argeriou, M. (1992). The Fifth Edition of the Addiction Severity Index. *Journal of Substance Abuse Treatment, 9*(3), 199-213.

Melinder, A., Konijnenberg, C., & Sarfi, M. (2013). Deviant smooth pursuit in preschool children exposed prenatally to methadone or buprenorphine and tobacco affects integrative visuomotor capabilities. *Addiction, 108*(12), 2175-2182. doi:10.1111/add.12267

Moe, V. (2002). Foster-placed and adopted children exposed in utero to opiates and other substances: Prediction and outcome at four and a half years. *Journal of Developmental and Behavioral Pediatrics, 23*(5), 330-339. doi:10.1097/00004703-200210000-00006

Moe, V., & Slinning, K. (2001). Children prenatally exposed to substances: Gender-related differences in outcome from infancy to 3 years of age. *Infant Mental Health Journal, 22*(3), 334-350. doi:10.1002/imhj.1005

Moe, V., & Slinning, K. (2002). Prenatal drug exposure and the conceptualization of long-term effects. *Scandinavian Journal of Psychology, 43*(1), 41-47. doi:10.1111/1467-9450.00267

Monk, C., Spicer, J., & Champagne, F. A. (2012). Linking prenatal maternal adversity to developmental outcomes in infants: the role of epigenetic pathways. *Development and Psychopathology, 24*(4), 1361-1376. doi:10.1017/s0954579412000764

Pajulo, M., Pyykkonen, N., Kalland, M., Sinkkonen, J., Helenius, H., & Punamaki, R. L. (2011). Substance abusing mothers in residential treatment with their babies: postnatal psychiatric symptomatology and its association with mother-child relationship and later need for child protection actions. *Nord J Psychiatry, 65*(1), 65-73. doi:10.3109/08039488.2010.494310

Pajulo, M., Savonlahti, E., Sourander, A., Ahlqvist, S., Helenius, H., & Piha, J. (2001). An early report on the mother-baby interactive capacity of substance-abusing mothers. *Journal of Substance Abuse Treatment, 20*(2), 143-151.

Quesada, O., Gotman, N., Howell, H. B., Funai, E. F., Rounsaville, B. J., & Yonkers, K. A. (2012). Prenatal hazardous substance use and adverse birth outcomes. *Journal of Maternal-Fetal & Neonatal Medicine, 25*(8), 1222-1227. doi:10.3109/14767058.2011.602143

Sameroff, A. J., & Emde, R. N. (1989). *Relationship disturbances in early childhood: A developmental approach*: Basic Books (AZ).

Sameroff, A. J., & Chandler, M. J. (1975). Reproductive risk and the continuum of caretaking casualty. *Review of child development research, 4*, 187-244.

Secker-Walker, R. H., Vacek, P. M., Flynn, B. S., & Mead, P. B. (1998). Estimated gains in birth weight associated with reductions in smoking during pregnancy. *Journal of Reproductive Medicine, 43*(11), 967-974.

Shah, P. E., Robbins, N., Coelho, R. B., & Poehlmann, J. (2013). The paradox of prematurity: the behavioral vulnerability of late preterm infants and the cognitive susceptibility of very

preterm infants at 36 months post-term. *Infant Behavior & Development, 36*(1), 50-62. doi:10.1016/j.infbeh.2012.11.003
Siqveland, T., Olafsen, K. S., & Moe, V. (2013). The influence of maternal optimality and infant temperament on parenting stress at 12 months among mothers with substance abuse and psychiatric problems. *Scandinavian Journal of Psychology, 54*(5), 353-362. doi:10.1111/sjop.12063
Siqveland, T., Smith, L., & Moe, V. (2012). The impact of optimality on maternal sensitivity in mothers with substance abuse and psychiatric problems and their infants at 3 months. *Infant Behavior & Development, 35*(1), 60-70. doi:10.1016/j.infbeh.2011.09.004
Slinning, K. (2004). Foster placed children prenatally exposed to poly-substances: Attention-related problems at ages 2 and 4 12. *European Child and Adolescent Psychiatry, 13*(1), 19-27. doi:10.1007/s00787-004-0350-x
Strand, B. H., Dalgard, O. S., Tambs, K., & Rognerud, M. (2003). Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nordic journal of psychiatry, 57*(2), 113-118.
Verheul, R. (2001). Co-morbidity of personality disorders in individuals with substance use disorders. *European Psychiatry, 16*(5), 274-282. doi:10.1016/S0924-9338(01)00578-8
Walhovd, K. B., Bjørnebekk, A., Haabrekke, K., Siqveland, T., Slinning, K., Nygaard, E., . . . Moe, V. (2015). Child Neuroanatomical, Neurocognitive, and Visual Acuity Outcomes With Maternal Opioid and Polysubstance Detoxification. *Pediatric Neurology, 52*(3), 326-332.
Wechsler, D. (2008). Wechsler preschool and primary scale of intelligence-III (WPPSI-III). Norwegian version: Stockholm, Sweden: Pearson Assessment.

Table 1 Maternal substance use per trimester per group

	Mothers with substance abuse problems (*n*=20[1])						**Mothers with mental health problems (*n* =17[1])**						**Low-risk comparison mothers (*n* =26)**					
	1.trimester		2.trimester		3.trimester		1.trimester		2.trimester		3.trimester		1.trimester		2.trimester		3.trimester	
Substance	*n*	%	*n*	%	*n*	%	*n*	%	*n*	*n*	%	*n*	*n*	%	*n*	*n*	%	*n*
Opiates [2]	11	55.0	5	25.0	2	10.0	0	0	0	0	0	0	0	0	0	0	0	0
Benzodiazepines	12	60.0	5	25.0	1	5.0	1	5.9	1	5.9	0	0	0	0	0	0	0	0
Cannabis	12	60.0	3	15.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Amphetamines	9	45.0	1	5.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Alcohol[3]	1	5.0	0	0	0	0	1	5.9	0	0	0	0	3	11.5	0	0	0	0
Alcohol binge[4]																		
More than once a week	1	5.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Once a week	0	0	0	0	0	0	1	5.9	0	0	0	0	1	3.8	0	0	0	0
1-3 times a month	2	10.0	0	0	0	0	2	11.8	0	0	0	0	1	3.8	0	0	0	0
Less than once a month	2	10.0	0	0	0	0	1	5.9	0	0	0	0	4	15.4	1	3.8	1	3.8
Nicotine daily	19[5]	100	19	100	14	73.7	5	29.4	5	29.4	3	17.6	1	3.8	0	0	0	0

[1] missing data for one mother [2]twice a month or more [3] Light drinking once a week or more [4]drinking 5 or more units on the same occasion [5]one missing

Table 2 Birth weight and caregiver characteristics at age 4 ½

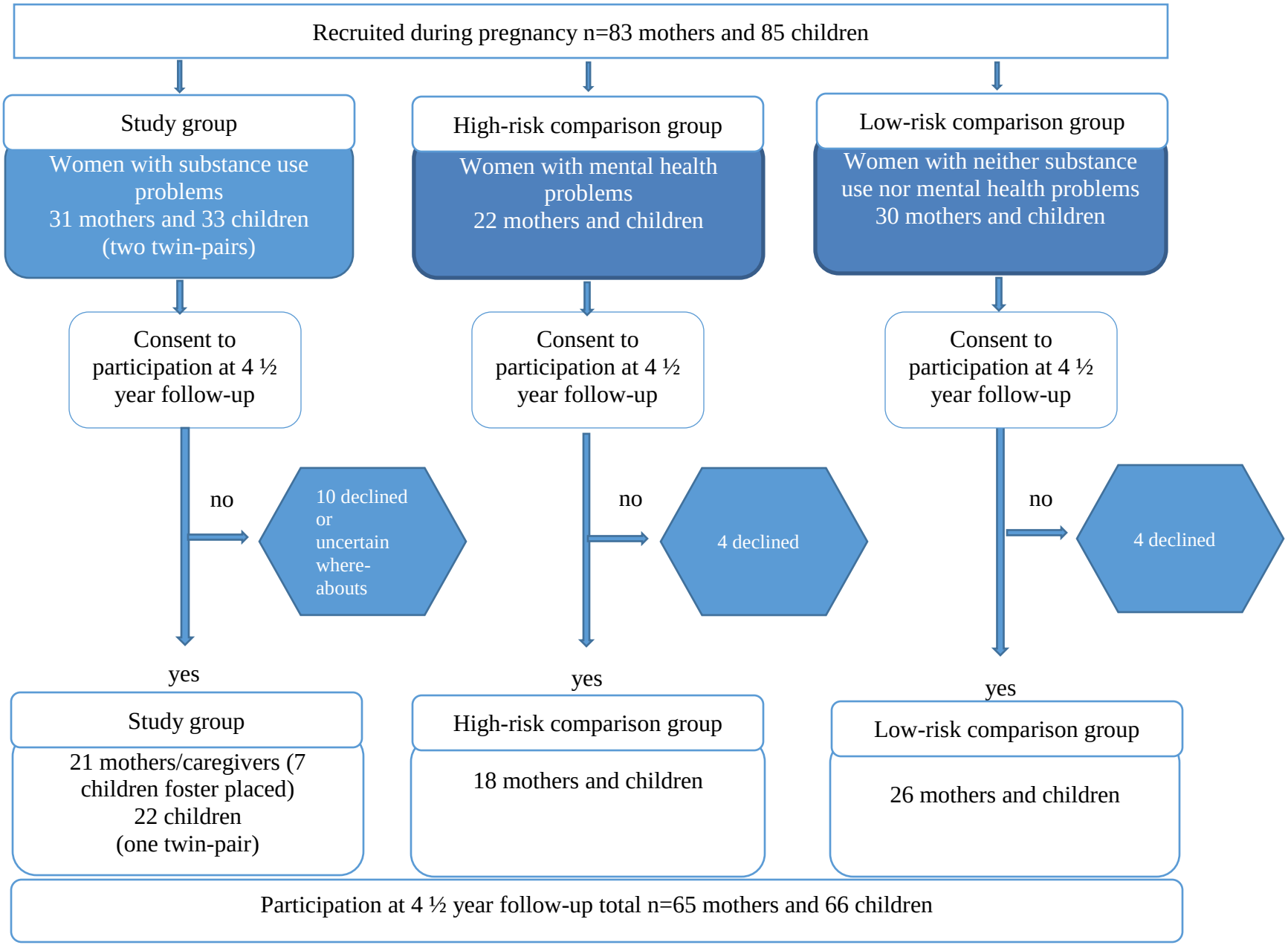
	Children born to mothers with substance abuse problems (*n*=22, 11 M[1])			**Children born to mothers with mental health problems (*n*=18, 7 M[1])**			**Low-risk comparison children (*n*=26, 16 M[1])**					
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	F	*p*	*Partial Eta*[2]
Birth weight (g)	3355	392	2450-3960	3343	619	1740-4132	3802	378	3060-4715	6.94[4]	.002[4]	0.18
Caregiver anxiety and depression at child age 4 ½[2]	8.0	9.8	0-42	24.2	22.4	2-90	3.7	2.9	0-10	13.53	<.001	0.31
	n	**%**		***n***	**%**		***n***	**%**		Chi[2]	*p*	*Pearson's cont.coef.*
Foster placement at age 4 ½	7	31.8		0	0		0	0		15.66	<.001	0.44
Single parenting[3]	10	47.6		2	11.1		2	7.7		12.56	.002	0.40
Caregiver education[3]										28.45	<.001	0.55
≤9 years	3	14.3		0	0		0	0				
10-11 years	3	14.3		2	11.1		0	0				
12 years	7	33.3		2	11.1		3	11.5				
college/university <4 years	7	33.3		8	44.4		5	19.2				
college/university ≥4 years	1	4.8		6	33.3		18	69.2				

[1] males [2] Group 1, *n*=21, group 2, *n*=17, group 3, *n*= 26 [3] Group 1, *n*=21, group 2, *n*=18, group 3, *n*= 26 [4] adjusted for gender

Table 3 Cognitive and socio-emotional development by group

	Children born to mothers with substance abuse problems (*n*=22)		**Children born to mothers with mental health problems (*n*=18)**		**Low-risk comparison children (*n*=26)**			
	Mean	SD	Mean	SD	Mean	SD	F[7]	*p*
WPPSI-III[1] Full Scale IQ	95.0	9.5	97.8	11.0	100.4	8.5	2.659	.078
Verbal IQ	98.4	9.6	100.3	12.0	101.9	8.8	.808	.450
Performance IQ	94.8	10.8	95.9	12.1	100.2	9.1	2.699	.075
Speed[2]	95.1	10.3	97.9	7.1	99.9	10.1	1.752	.182
Receptive language[2]	99.2	7.8	101.2	10.3	101.2	11.1	.307	.737
CBCL[3] total[4]	31.9	27.9	29.6	14.3	15.5	10.9	4.920	.011
CBCL[3]internalizing[4]	9.6	9.2	8.4	5.6	3.4	3.3	5.630	.006
CBCL[3]externalizing[4]	11.3	9.5	9.9	5.2	6.6	4.7	2.744	.073
TRF[5] total[6]	19.7	19.5	15.1	10.4	24.0	21.0	.938	.397
TRF[5] Internalizing[6]	9.9	5.7	5.2	3.7	6.0	5.3	.120	.887
TRF[5] Externalizing[6]	9.4	12.2	6.1	5.9	12.1	13.6	1.009	.371

[1] Wechsler Preschool and Primary Scale of Intelligence, third edition. [2]Group 1, *n*=22, group 2, *n*=17, group 3, *n*=26. [3]Child Behavior Check List. [4]Group 1, *n*=22, group 2, *n*=16, group 3, *n*=26. [5] Teachers Report Form. [6]Group 1, *n*=21, group 2, *n*=15, group 3, *n*= 24. [7]F and p values are for the effect of group when gender and age are entered as covariates in linear regression analyses. For WPPSI-III, only gender was entered as covariate as standardized scores are rated according to age.


Recruited during pregnancy n=83 mothers and 85 children
Study group
Women with substance use problems
31 mothers and 33 children
(two twin-pairs)
High-risk comparison group
Women with mental health problems
22 mothers and children
Low-risk comparison group
Women with neither substance use nor mental health problems
30 mothers and children
Consent to participation at 4 ½ year follow-up
Consent to participation at 4 ½ year follow-up
Consent to participation at 4 ½ year follow-up
no
10 declined or uncertain where-abouts
no
4 declined
no
4 declined
yes
yes
yes
Study group
21 mothers/caregivers (7 children foster placed)
22 children
(one twin-pair)
High-risk comparison group
18 mothers and children
Low-risk comparison group
26 mothers and children
Participation at 4 ½ year follow-up total n=65 mothers and 66 children