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van der Veere, Christine N; de Vries, Nathalie K S; van Braeckel, Koenraad N J A; Bos, Arend F

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Intra-uterine exposure to selective serotonin reuptake inhibitors (SSRIs), maternal psychopathology, and neurodevelopment at age 2.5years — Results from the prospective cohort SMOK study

Christine N. van der Veere*[,1], Nathalie K.S. de Vries[2], Koenraad N.J.A. van Braeckel, Arend F. Bos

Department of Pediatrics, University of Groningen, University Medical Center Groningen, the Netherlands

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ABSTRACT

Background: Selective serotonin reuptake inhibitors (SSRIs) are prescribed in 2–8% during pregnancy. Whether prenatal exposure to SSRIs has long-term effects on the children's development is unknown.
Aim: The aim of this study was to determine the effect of prenatal exposure to SSRIs on children's cognitive, motor, and behavioral outcomes at 2.5 years, adjusted for maternal depression and anxiety.
Methods: In a prospective, longitudinal cohort-study we included 111 pregnant women treated either or not with an SSRI. We examined cognitive and motor development of their children at 2.5 years, using the Bayley Scale of Infant and Toddler Development, 3rd Edition, and measured emotional and behavioral problems using the parent-rated Child Behavior Checklist (CBCL). Maternal depression and anxiety was determined during pregnancy and at the children's assessment. Differences of normed cognitive, motor, and behavioral scores between SSRI-exposed and non-SSRI-exposed children were tested using multiple linear regression analyses.
Results: We examined 102 children. SSRI-exposed children had lower scaled scores on cognition and gross motor development than non-SSRI-exposed children: 9.0 ± 1.4 (mean ± SD) versus 9.9 ± 1.7 [$P = 0.004$], and 7.9 ± 2.2 versus 9.0 ± 2.5 [$P = 0.01$], respectively. Differences remained significant after adjusting for maternal depression and anxiety and other confounders in various models (mean difference for cognition 0.8 to 0.9 points, for gross motor 1.1 to 1.2 points). Only after adjusting for *severity* of maternal anxiety, differences in gross motor scores lost significance.
Conclusions: Prenatal exposure to SSRIs is associated with poorer cognitive and gross motor development of the children at 2.5 years. Effects on gross motor development disappeared after correction for severity of maternal anxiety.

1. Introduction

Approximately 10% to 25% of pregnant and postpartum women are diagnosed with a major depression [1]. Anxiety is present in approximately 20% [2]. Symptoms of depression and anxiety often overlap [3]. Depression during pregnancy is known to have adverse effects on the development of the child, including preterm birth and lower birth weight [4]. Children are more vulnerable to develop cognitive problems and adverse behavior [4,5].

Depression and anxiety are treated with medication, also during pregnancy. Selective serotonin reuptake inhibitors (SSRIs) are most often prescribed. Prescription rates during pregnancy range from 2% in the Netherlands [6] to 8% in the USA [7]. SSRIs cross the placenta readily [8]. Following intra-uterine exposure to SSRIs, researchers have reported a higher incidence of adverse effects directly after birth. These include low birth weight, preterm birth, admission to a neonatal intensive care unit, tremors, and feeding difficulties [9,10]. Concern on the effects of SSRIs on the developing brain first came from animal studies. They showed irreversible changes to neuronal networks in the brain and altered behavior in offspring following intra-uterine exposure to SSRIs [11]. Serotonergic neurons project to the forebrain and are thus related to cognitive functions, but serotonin is also related to the

Abbreviations: SSRI, selective serotonin reuptake inhibitor; SS, Scaled scores; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; BSID, Bailey Scales of Infant and Toddler Development; CBCL, Child Behavior Checklist; IUGR, intra-uterine growth restriction; STAI-T, State Trait Anxiety Inventory-Trait

* Corresponding author at: Wilhelmina Hospital Assen, Department of Pediatrics, PO Box 30.001, 9400 RA Assen, the Netherlands.
E-mail addresses: christa.vanderveere@wza.nl, c.n.van.der.veere@umcg.nl (C.N. van der Veere).
[1] Present address: Department of Pediatrics, Wilhelmina Hospital Assen, the Netherlands.
[2] Present address: Department of Pediatrics, MidCentral Health, Palmerston North, New Zealand.

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motor system of the brain and to brain regions critical to emotional processing [12].

Data in humans are consistent with animal studies regarding short-term effects. Recently three studies reported on human newborn brain function, structure and connectivity patterns following intra-uterine SSRI exposure [13–15]. Using EEG recordings, a reduced interhemispheric connectivity and reduced frontal activity was reported in newborns [13]. MRI-analyses of neonatal brain volumes revealed widespread changes in white matter microstructure in SSRI-exposed neonates [14]. In infants 3 to 4 weeks old, prenatal SSRI exposure was associated with altered fetal brain development, particularly in brain regions critical to emotional processing [15].

Studies on long-term effects in humans are fragmented and inconclusive (for review see El Marroun et al. [16]). Moreover, not all studies take maternal depression and anxiety into account when analyzing their data. Cognitive development seems to be within the normal range in most studies and not different between SSRI-exposed children and controls [17–19]. Nulman et al. were the first to report that the IQs of SSRI-exposed children were significantly lower than that of non-SSRI exposed children at age 3 to 7 years [20]. Regarding motor development, some studies reported no or minor associations between antenatal SSRI exposure and motor outcome [18,21], others reported negative associations with motor development [22,23]. Clear evidence for delayed cognitive or motor development is not yet available. An increase in prevalence rates of depressive symptoms [24], Autism Spectrum Disorders [25], and Attention Deficit Hyperactivity Disorder [26] has been reported in children.

Additional research is needed to clarify the potential effects of prenatal exposition to SSRIs on development of children on the long term, preferably controlled for maternal depression and anxiety. The aim of our longitudinal study was to determine neurodevelopmental outcome after prenatal SSRI exposure, regarding the motor domain, cognition and behavior, at age 3 months, 2.5 years and 7–8 years, adjusted for maternal depression and anxiety. Thus far, we published results on early neurological functioning up to the age of 3 months [10]. In the present study we report on neurodevelopmental outcome of the children in the same cohort, at age 2.5 years.

2. Patients and methods

2.1. Design

To investigate long-term development in humans following SSRI-exposure, we initiated a prospective study in 2006. We chose a prospective, longitudinal cohort design for the Dutch 'SSRI in pregnant mothers, outcome of the kids' study, abbreviated to SMOK [10]. Originally, we intended to compare three study groups: the SSRI group, women who reported depression and/or anxiety without using medication, and healthy controls (Fig. 1). During the inclusion process, however, it appeared that few pregnant women were referred to the second study group. Additionally, it appeared that the healthy control group also comprised women with a positive score on depression or anxiety questionnaires. We therefore merged these two groups, resulting in one cohort, the non-SSRI group. This non-SSRI group is not a normal control group, because the prevalence of maternal mental health problems is higher than in the general population. However, this enabled us to compare the development of children who had been exposed to an SSRI during pregnancy to the development of children who had not been exposed, with adjustment for maternal psychopathology.

The Medical Ethics Committee of University Medical Center Groningen, the Netherlands, approved the study protocol and the consent procedure. The study was registered in the International Standard Randomized Controlled Trial registry under number 53506435.

2.2. Subjects

Pregnant women, living in the vicinity of two Level-2 hospitals in the Northern part of the Netherlands were recruited via newspapers, midwifes, general practitioners, gynecologists, and psychiatrists between May 2007 and April 2010. Written informed consent by both future parents was obtained.

2.3. Inclusion and exclusion criteria

The inclusion criteria for the SSRI group were treatment with SSRIs for depression and/or anxiety disorder during pregnancy and already taking this medication before conception. We also registered which SSRIs were prescribed. Venlafaxine was considered to work as an SSRI if given in low doses [27]. Women taking < 200 mg venlafaxine were included in the SSRI group. Women who had stopped taking medication before delivery (n = 4, stopped in week 6, 15, 23 and 36 of pregnancy, respectively) remained in the SSRI group. Exclusion criteria were the use of psychotropic drugs other than SSRIs, anti-epileptic drugs, and multiple congenital anomalies of the infant.

The inclusion criterion for the non-SSRI group was no psychotropic medication during pregnancy. Exclusion criteria were maternal treatment with anti-epileptic drugs and, in the case of the infant, multiple congenital anomalies. Eventually, we included 111 mother-infant pairs.

2.4. Definition of maternal depression, anxiety, and psychopathology

Maternal depression and anxiety were measured during the third trimester of pregnancy and when the child was 2.5 years old, using the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI) [28,29]. The BDI is a self-reported, 21-item questionnaire measuring depressive symptoms (scores 0 to 63). Depression was defined by a BDI score of more than or equal to 13 [28]. The STAI is a self-reported, 20-item questionnaire measuring temporary anxiety state conditions (STAI-S) and anxiety trait conditions (STAI-T) (scores 20 to 80) [29]. For the present study we chose to use the STAI-T for anxiety during pregnancy and at the assessment age of 30 months, as we know that maternal anxiety has important effects on infant and child development and the trait score reflects how a person generally feels, marking anxiety as a personal characteristic. Anxiety was defined as a STAI-T score of > 40 [29]. Maternal psychopathology was defined as a score consistent with depression on the BDI and/or anxiety on the STAI-T.

2.5. Measurements

We assessed 102 children at age 2.5 years using the Bayley Scales of Infant and Toddler Development (BSID), 3rd Edition (cognitive, fine motor, and gross motor scales) [30]. The BSID was performed in one of the two level-2 hospitals under standardized conditions as described in the manual. Scaled scores (SS) were derived from total raw scores for each subtest and used for analysis because scaled scores are corrected for the child's age at the date of testing. Scaled scores range from 1 to 19, with a mean of 10 (equivalent to the median) and an SD of 3. The examiner was blinded for maternal mental state and use of SSRI during pregnancy.

We asked the parents to fill out the Child Behavior Checklist (CBCL) - Dutch version for ages 1.5 to 5 years [31]. The CBCL is a screening tool for emotional, behavioral, and social problems. The preschool checklist contains 100 questions, which are sorted in seven syndrome scales: Emotionally Reactive; Anxious/Depressed; Somatic Complaints; Withdrawn (those 4 scales are separately analyzed as Internal Problems); Attention Problems; Aggressive Behavior (those 2 scales are separately analyzed as External Problems), Sleep Problems and Other Problems. The Total Problems score is the sum of the scores of all the items. The CBCL uses a normative sample to create standard scores, i.e. T-scores,

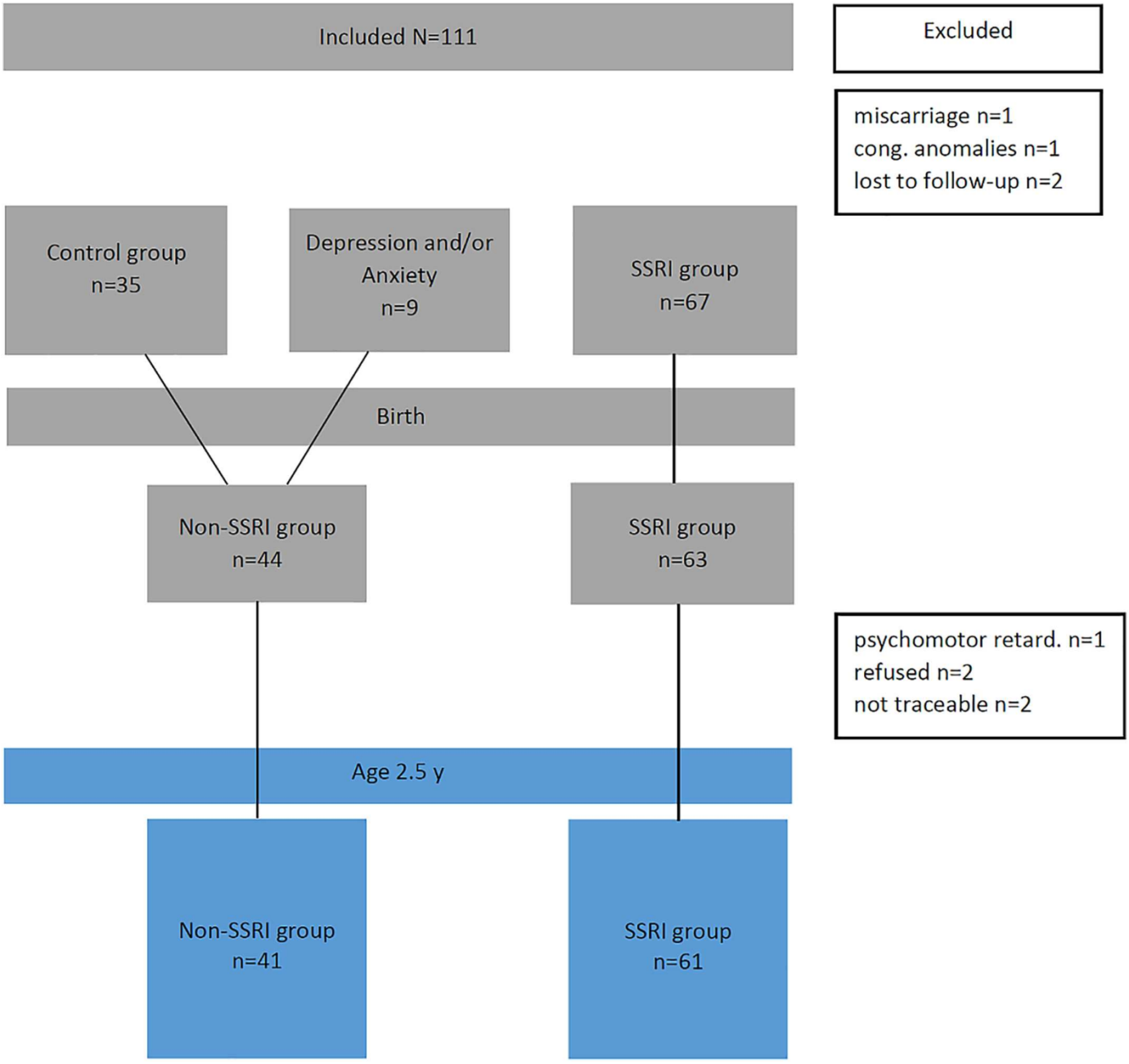

Fig. 1. Study design and flow chart of included children. Abbreviations: cong., congenital; retard., retardation.

which we used for our analyses. Higher scores indicate more problems [31]. The questionnaires were administered by letter, filled out at home and handed in at the date of assessment.

2.6. Statistical analysis

We estimated that we needed to include at least 105 children to have sufficient statistical power to analyze the effects of SSRIs with two reference groups (i.e. two dummy variables) and five potential confounding variables on our primary outcome measure. Such an analysis would yield seven dichotomous variables with 15 participants per comparison. This was a conservative estimate of ten events per dichotomized predictive variable plus a 50% buffer [32]. As explained, we later decided to split the group in two, yielding one study group (maternal exposure to SSRIs) and one control group (no maternal exposure to SSRIs).

Data were analyzed using SPSS 22. First, we calculated descriptive statistics, frequencies, and normality of distribution to decide whether to apply parametric or nonparametric statistical tests. For analyses of differences regarding background characteristics we performed Fisher's exact test for categorical data, Student's *t*-tests for birth weight and gestational age, and Mann Whitney-*U* tests for all other continuous variables. Differences were considered statistically significant at $P < .05$, two-tailed.

Second, we calculated the mean and SD of the scores on the BSID and CBCL in our cohort separately for the SSRI-exposed and the non-SSRI exposed children, and tested statistically significant differences using student's *t*-tests. Within the group of SSRI-exposed children, we analyzed the effect of paroxetine separately as paroxetine was prescribed most often in our study. Next we calculated the mean and SD of the scores categorizing our cohort by maternal psychopathology (that is depression and/or anxiety) during the third trimester of pregnancy and

by maternal psychopathology at assessment age. Again, statistically significant differences of the scores in these subgroups were determined using student's *t*-tests.

Third, we performed multiple linear regression analyses. We checked for multicollinearity before entering multiple variables into a single multivariable model, and if present, we decided to construct separate multivariable regression models. Because the BDI scores and STAI-T scores correlated strongly with each other, both at and in between time points, we constructed two models regarding maternal psychopathology, one with maternal psychopathology during pregnancy, and the other with maternal psychopathology at assessment age as one of the confounders.

Apart from maternal psychopathology, we considered the following confounders important for the relation between maternal SSRI exposure and cognitive development: maternal education, gender, gestational age, birth weight, intra-uterine growth restriction, asphyxia (defined as Apgar score at 5 min below 5), maternal smoking and exposure to alcohol during pregnancy. Maternal education was defined as high when the mothers had attended college or university. Low-level education was defined as: attended vocational education and training, high school, or lower. We decided to include gender and maternal education in all multiple regression analyses as confounder. The other potential confounders were first tested in univariate analyses, and were only included in the multiple regression analyses if they were related to the children's outcome with $P < 0.05$. Only birth weight was included. Gestational age, intrauterine growth retardation, asphyxia, maternal smoking and exposure to alcohol were not related to outcome and were omitted from multiple regression analyses.

Finally, for a better understanding of the confounding effects of the *severity* of maternal depression and anxiety on the association between SSRI exposure and neurodevelopmental outcome scores, we repeated the multiple regression analyses with continuous BDI and STAI scores for the outcome measures that were significantly different in the univariate analyses (meaning cognition and gross motor outcome), in four separate models, to avoid multicollinearity.

As almost all the fathers scored normal on the BDI and STAI questionnaires, paternal data were not included in the analyses.

3. Results

Initially 111 mother-infant couples were included in the study. Four mother-infant pairs could not be included after birth, so we started with 107 mother-infant pairs (Fig. 1).

At the age of 2.5 years, we performed developmental tests in 102 children, a follow-up rate of 95%. Reasons for the five exclusions were psychomotor retardation *e causa ignota* (n = 1, from the control group), moved to an unknown new address (n = 2), and refusal (n = 2). Two of the children lost to follow-up were from the SSRI group and three were from the non-SSRI group. All children were tested between November 2009 and September 2012, between the ages of 28 months 12 days and 35 months 19 days.

We had no missing data on the BSID, apart from three children due to non-compliance regarding the gross motor score. Missing data for the CBCL amounted to 10 out of 102. These parents, nine from the SSRI group and one from the non-SSRI group, had failed to fill out the CBCL or had done so incompletely. Two out of 102 mothers also did not fill out the BDI and STAI around the time the children were tested. We do not know whether mothers with mental illness, or women with more challenging children had a greater challenge in submitting the paperwork and perhaps failed to do so.

3.1. Background characteristics

In Table 1, we present the mothers' and children's background characteristics, including data on maternal depression and/or anxiety during pregnancy and at assessment age. All women had a Caucasian background. No significant differences were found between the groups in maternal background characteristics. During pregnancy, scores on the BDI were marginally higher in the SSRI-group, suggesting more severe depression in the SSRI-group. Scores on the STAI-T were considerably higher in the SSRI-group. At the age of assessment, at 2.5 years of the child, the scores on the BDI were not significantly different, but scores on the STAI-T were still higher in the SSRI-group. The presence or absence of maternal psychopathology in pregnancy and at assessment age of the child changed in 20 mothers. At the assessment age of the child, psychopathology had disappeared in 10 mothers, and had newly appeared in 10 others.

In Table 2, we present the type and daily dose of the SSRI the mothers were taking. Most women were treated with paroxetine (44%).

Table 1
Background characteristics of the women and children.

	SSRI group (n = 61)	Non-SSRI group (n = 41)	*P*-value[a]
Women's general characteristics			
Age at labor, years, median (min-max)	31 (24–42)	32 (22–39)	0.753[x]
Cesarean section, n (%)	5/61 (8)	4/41 (10)	1.000[y]
Low-level education[b], n (%)	25/55 (45)	15/40 (38)	0.529[y]
Alcohol use > 2 units/week, n (%)	3/56 (5)	0/40 (0)	0.270[y]
Smoking, n (%)	11/56 (20)	3/40 (8)	0.143[y]
Cigarettes per day among smokers, median (min-max)	6 (1 – 20)	5 (5–10)	1.000[x]
Children's general characteristics			
Gestational age, weeks, mean ± SD	39.4 ± 1.3	39.9 ± 1.1	0.053[z]
Birth weight, grams, mean ± SD	3438 ± 588	3805 ± 478	**0.008[z]**
Male sex, n (%)	26/61 (43)	20/41 (49)	0.551[y]
Preterm, n (%)	3/58 (5)	0/41 (0)	0.272[y]
IUGR (birth weight < P_{10}), n (%)	10/60 (17)	2/40 (5)	0.117[y]
Apgar score ≤ 5 at 5 min, n (%)	2/59 (3)	0/37 (0)	0.521[y]
Age at follow-up, months, median (min-max)	30.1 (29.0–35.2)	30.1 (28.1–34.1)	0.863[x]
Maternal psychopathology during pregnancy			
BDI score, median (min-max)	7 (0–34)	4 (0–35)	**0.050[x]**
STAI-T score, median (min-max)	40 (25–70)	27.5 (20–68)	**< 0.001[x]**
Depression, n (%)	14/59 (26)	9/41 (22)	1.000[y]
Anxiety trait, n (%)	28/58 (48)	8/40 (20)	**0.005[y]**
Psychopathology[c], n (%)	30/59 (49)	9/41 (22)	**0.004[y]**
Maternal psychopathology at assessment age of her child (2.5 years)			
BDI score, median (min-max)	5 (0 – 32)	3 (0–36)	0.175[x]
STAI-T score, median (min-max)	36 (22–73)	30 (20–69)	**0.002[x]**
Depression, n (%)	14/60 (23)	6/40 (15)	0.445[y]
Anxiety trait, n (%)	24/59 (39)	9/41 (22)	0.056[y]
Psychopathology[c], n (%)	24/60 (39)	10/41 (24)	0.134[y]

IUGR, intra-uterine growth restriction; BDI, Beck Depression Inventory; STAI-T, State Trait Anxiety Inventory-Trait.
Bold font signifies statistical significant differences.
[a] Statistical test used: [x] Mann Whitney-*U* test; [y] Fisher's exact test; [z] Student's *t*-test.
[b] Low-level education: secondary vocational education and training, high school, or lower.
[c] Maternal depression and/or anxiety, based on abnormal scores on BDI for depression or STAI-T for anxiety.

3.2. Cognitive outcome

We present the scores on the BSID and CBCL of SSRI-exposed and non-SSRI exposed children in Table 3, together with the scores when categorizing our cohort by maternal psychopathology (depression and/

Table 2
Types and doses of SSRIs administered.

Type of SSRI	n (%)	Daily dose (mg)
Paroxetine	27 (44)	10–40
Cipramil	13 (21)	10–30
Venlafaxine	9 (15)	37.5–150
Fluoxetine	8 (13)	10–40
Sertraline	2 (3)	50–100
Changed medication	2 (3)	

or anxiety) during the third trimester of pregnancy and at assessment age. Scaled scores for cognition were lower in the SSRI-exposed children than in non-SSRI exposed children. As paroxetine was prescribed most frequently, we separately analyzed the results for paroxetine and compared them with those of the other SSRIs. Cognitive outcome was not significantly different between paroxetine exposed children and children exposed to another SSRI. When maternal psychopathology was present during pregnancy, cognitive scores of the child were lower and this was the same for maternal psychopathology at assessment age.

3.3. Gross motor outcome

Scaled scores of gross motor skills were lower in SSRI-exposed children than in non-SSRI exposed children. Gross motor outcome was not different between paroxetine exposed children and children exposed to another SSRI. Presence of maternal psychopathology during pregnancy or at age of assessment did not result in differences in gross motor scores of the children (Table 3).

3.4. Fine motor outcome

Scaled scores of fine motor skills did not differ between the SSRI and non-SSRI groups. Fine motor outcome was not different between paroxetine exposed children and children exposed to another SSRI. Presence of maternal psychopathology during pregnancy did not result in differences in fine motor scores of the children. When maternal psychopathology was present at the children's assessment age, fine motor scores of the child were lower (Table 3).

3.5. Behavioral outcome

The T-scores on the CBCL were not different between the SSRI and non-SSRI groups. Behavioral outcome was not different between paroxetine exposed children and children exposed to another SSRI. Presence of maternal psychopathology during pregnancy did not result in differences in behavioral scores of the children. When maternal psychopathology was present at the children's assessment age, T-scores on the CBCL total score, internalizing scale and externalizing scale were higher, indicating more behavioral problems (Table 3). Both anxiety and depression at assessment age were related to higher CBCL scores, with anxiety showing the largest differences.

3.6. SSRI-exposure, maternal depression and anxiety, other confounders

The presence of maternal psychopathology may confound the relation between prenatal SSRI exposure and outcome of the children. To address this issue we performed multiple regression analyses adjusting for maternal psychopathology, both during the last trimester of pregnancy and at the time the children were assessed. The Spearman's rho correlation coefficients between the scores on the BDI and STAI-T at the various time points were high (Table 4). To avoid multicollinearity we therefore constructed two multiple regression models. Other potential confounders we entered in the models were gender and maternal education. Because birth weight was significantly lower in the SSRI group we also entered this variable in the models as confounder.

We present the mean differences between SSRI exposure versus non-SSRI exposure in BSID and CBCL scores of the children at the age of 2.5 years in Table 5, both unadjusted and adjusted for gender, maternal education, birth weight, and maternal psychopathology during pregnancy (model 1) or at assessment age (model 2). After adjustment, entering maternal psychopathology as a categorical variable, the relation between exposure to SSRI and poorer cognitive scores remained statistically significant. The relation between exposure to SSRI and poorer gross motor scores remained statistically significant when

Table 3
Scores on cognition, motor domains and behavior at age 2.5 years, in relation to SSRI exposure, maternal psychopathology in pregnancy and maternal psychopathology at 2.5 years (univariate analyses).

	SSRI exposure during pregnancy				Maternal psychopathology[3] during pregnancy[¶]		Maternal psychopathology[3] at the children's age of 2.5 years[¶]	
			Type of SSRI					
	Yes n = 61	No n = 41	Paroxetine n = 27	other SSRI n = 34	Yes n = 34	No n = 67	Yes n = 34	No n = 67
BSID[1] Cognition	**9.0 ± 1.4****	**9.9 ± 1.7**	8.9 ± 1.0	9.1 ± 1.6	**8.8 ± 1.6***	**9.7 ± 1.5**	**8.8 ± 1.6****	**9.7 ± 1.5**
BSID Gross motor	**7.9 ± 2.2***	**9.0 ± 2.5**	7.7 ± 2.4	8.2 ± 2.0	8.0 ± 2.3	8.5 ± 2.4	7.9 ± 2.2	8.6 ± 2.4
BSID Fine motor	10.2 ± 2.2	10.6 ± 2.4	10.3 ± 2.3	10.2 ± 2.3	10.1 ± 2.1	10.5 ± 2.4	**9.6 ± 2.1****	**10.8 ± 2.3**
CBCL[2] total	47.0 ± 10.4	44.1 ± 7.8	47.0 ± 10.3	46.9 ± 10.7	48.1 ± 8.7	44.6 ± 9.5	**50.8 ± 10.4****	**43.2 ± 7.9**
CBCL internalizing	46.3 ± 10.1	43.2 ± 8.7	46.5 ± 11.5	46.1 ± 9.1	46.8 ± 8.5	44.2 ± 9.9	**49.3 ± 9.7****	**42.9 ± 8.9**
CBCL externalizing	49.4 ± 11.4	47.8 ± 8.1	48.7 ± 10.1	49.8 ± 12.4	51.0 ± 10.1	47.5 ± 10.0	**53.6 ± 11.9****	**46.2 ± 8.0**

BSID, Bayley Scales of Infant and Toddler Development; CBCL, Child Behavior Checklist.
Note: these groups were created irrespective of SSRI exposure, and comprised different individuals for various time-points.
Bold font signifies statistical significant differences.
[¶] Note: these groups were created irrespective of SSRI exposure, and comprised different individuals for various time-points.
[1] BSID: scaled score, mean ± SD
[2] CBCL: T-score, mean ± SD
[3] Maternal depression and/or anxiety, based on abnormal scores on BDI for depression or STAI-T for anxiety, entered as categorical variable
* $P \leq 0.05$, two-tailed, student's t-test
** $P \leq 0.01$, two-tailed, student's t-test

Table 4
Correlation matrix of BDI scores and STAI-T scores during pregnancy and at assessment age at 2.5 years. Data presented as Spearman's rho correlation coefficients, and corresponding *P*-values.

	BDI during pregnancy	BDI at assessment age 2.5 years	STAI-T during pregnancy
BDI at assessment age 2.5 years	**0.619** ***P*** **< 0.001**	-	
STAI-T during pregnancy	**0.747** ***P*** **< 0.001**	**0.578** ***P*** **< 0.001**	-
STAI-T at assessment age 2.5 years	**0.652** ***P*** **< 0.001**	**0.757** ***P*** **< 0.001**	**0.782** ***P*** **< 0.001**

BDI, Beck Depression Inventory; STAI-T, State Trait Anxiety Inventory-Trait.

adjusted for maternal psychopathology during pregnancy but became non-significant when adjusted for maternal psychopathology at assessment age. The mean differences of fine motor scores and behavioral scores between maternal SSRI exposure versus non-SSRI exposure did not reach statistical significance. We present the (adjusted) R^2 of the models to provide information on how much the confounders contribute to explaining the variance of the outcome. The adjusted R^2 is almost doubled for cognitive outcome when maternal psychopathology is added in the model, which indicates that both SSRI exposure and maternal psychopathology have impact on cognitive outcome. Of note, all differences pointed in one direction, whether adjusted or not and whether significant or not: poorer scores after exposure to SSRI in pregnancy (Table 5).

To test whether *severity* of maternal depression or anxiety influences the association between SSRI-exposure and outcome, we repeated the multiple regression analyses for cognition and gross motor skills with continuous BDI and STAI-T scores as confounders. To avoid multicollinearity, we tested four separate models and entered either BDI scores during pregnancy, STAI-T scores during pregnancy, BDI scores at assessment age, or STAI-T scores at assessment age in the model. Next we repeated these analyses, now also entering the other confounders in the models, that is gender, maternal education and birth weight. Entering gestational age in the models as potential confounder did not affect the analyses. The results are presented in Table 6. When adjusted for BDI-scores, differences between SSRI exposure versus non-SSRI exposure remained significant regarding cognition and gross motor outcome. When adjusted for STAI-T scores during pregnancy and at assessment age, differences between SSRI-exposed versus non SSRI exposed children remained significant regarding cognition, but lost significance regarding gross motor outcome (Table 6 upper part). When we additionally entered the other confounders the differences regarding both cognition and gross motor outcome lost significance in the models with the STAI-T scores as confounder, either during pregnancy or at assessment age (Table 6 lower part).

4. Discussion

Our study demonstrates that children who have been exposed to an SSRI during pregnancy show delayed cognitive and gross motor development at age 2.5 years. The effect remains after adjustment for confounding factors in nearly all models. Differences between the groups were approximately one-third SD, comparable with a developmental delay of around three months at this age. No relation was found between exposure to SSRI during pregnancy and fine motor outcome and emotional and behavioral problems.

It is well-known that the mother's mental state during pregnancy and after having given birth has an effect on cognitive development of the child [4]. In our study, we adjusted for detailed aspects of maternal mental state in pregnancy and at the child's assessment age of 2.5 years. We excluded multicollinearity and hereby demonstrated that SSRIs have an independent negative effect on cognitive development. The severity of anxiety, as measured by the maternal-reported STAI-T, was the only factor altering the significance of the relation between SSRI exposure and cognitive scores. Even so, the mean differences in scores were only slightly lower when severity of anxiety was included as confounder compared with all other multivariate models. Of note, the severity of maternal depression did not influence the association in our cohort.

In contrast to our findings, most studies in the past reported no differences in cognitive outcome between children exposed to antidepressant drugs and comparison groups or general population norms [17–19]. Several of these studies had methodological shortcomings as they were either not specifically designed to assess children's intelligence, lacked appropriate comparison groups, were underpowered, included other antidepressant medication like tricyclic antidepressants, or had a follow-up at very different ages using various neurodevelopmental tests. Moreover, only the study by Brown et al. adjusted for

Table 5
Mean differences between maternal SSRI exposure versus non-SSRI exposure regarding scores on cognition, the motor domain, and behavior at 2.5 years. Results are based on linear regression analyses, both unadjusted and adjusted for maternal psychopathology during pregnancy (Model 1) and at assessment age of 2.5 years (Model 2).

	SSRI exposure *Univariate*			SSRI exposure *Model 1*[1]			SSRI exposure *Model 2*[2]		
	B (95% CI)	beta	adj. R^2	B (95% CI)	beta	adj. R^2	B (95% CI)	beta	adj. R^2
BSID Cognition	**−0.9*** **(−1.5 to − 0.3)**	**−0.28**	**0.069**	**−0.8*** **(−1.4 to − 0.1)**	**−0.23**	**0.142**	**−0.8*** **(−1.4 to − 0.1)**	**−0.24**	**0.146**
BSID Gross motor	**−1.1*** **(−2.1 to − 0.2)**	**−0.23**	**0.044**	**−1.1*** **(−2.2 to − 0.1)**	**−0.24**	**0.032**	−1.1 (−2.2 to 0.02)	−0.22	0.027
BSID Fine motor	−0.4 (−1.3 to 0.5)	−0.09	−0.003	−0.2 (−1.2 to 0.8)	−0.05	0.053	−0.1 (−1.1 to 0.9)	−0.02	0.069
CBCL total	2.9 (−1.1 to 6.8)	0.15	0.012	3.4 (−1.0 to 7.8)	0.18	0.054	2.7 (−1.5 to 6.8)	0.14	0.137
CBCL internalizing	3.0 (−0.9 to 7.0)	0.16	0.014	2.9 (−1.7 to 7.6)	0.15	−0.022	2.0 (−2.5 to 6.4)	0.10	0.051
CBCL externalizing	1.6 (−2.6 to 5.8)	0.08	−0.005	2.1 (−2.5 to 6.6)	0.10	0.047	1.7 (−2.6 to 6.0)	0.08	0.128

BSID, Bayley Scales of Infant and Toddler Development; CBCL, Child Behavior Checklist; CI, confidence interval; adj., adjusted.
Bold font signifies statistical significant differences.
[1] Model 1: linear regression analyses, adjusted for maternal psychopathology during the third trimester of pregnancy (entered as categorical variable), low-level maternal education, birth weight and gender. Adjusted R^2 concerns the complete model. Method Enter.
[2] Model 2: linear regression analyses, adjusted for maternal psychopathology at child's age of 2.5 years (entered as categorical variable), low-level maternal education, birth weight and gender. Adjusted R^2 concerns the complete model. Method Enter.
* $P \leq 0.05$, two-tailed.

Table 6
Mean differences between maternal SSRI exposure versus non-SSRI exposure regarding scores on cognition, the motor domain, and behavior at 2.5 years. Results are based on linear regression analyses, adjusted for severity of depression/anxiety during pregnancy and at assessment age only (upper part), and adjusted for other confounders and for severity of depression/anxiety during pregnancy and at assessment age (lower part).

	SSRI exposure (unadjusted)		SSRI exposure Adjusted for BDI scores during pregnancy		SSRI exposure Adjusted for STAI-T scores during pregnancy		SSRI exposure Adjusted for BDI scores at assessment age		SSRI exposure Adjusted for STAI-T scores at assessment age	
	B (95% CI)	beta	B (95% CI)	beta	B (95% CI)	beta	B (95% CI)	beta	B (95% CI)	beta
BSID Cognition	**-0.9* (-1.5 to -0.3)**	**-0.28**	**-0.8* (-1.4 to -0.2)**	**-0.26**	**-0.7* (-1.3 to -0.03)**	**-0.21**	**-0.9* (-1.5 to -0.2)**	**-0.27**	**-0.7* (-1.3 to -0.04)**	**-0.21**
BSID Gross motor	**-1.1* (-2.1 to -0.2)**	**-0.23**	**-1.2* (-2.1 to -0.2)**	**-0.24**	-1.0 (-2.2 to 0.008)	-0.21	**-1.1* (-2.1 to -0.2)**	**-0.24**	-0.9 (-1.9 to 0.1)	-0.19

	SSRI exposure (unadjusted)		SSRI exposure Adjusted for BDI scores during pregnancy, birth weight, low maternal education and gender		SSRI exposure Adjusted for STAI-T scores during pregnancy, birth weight, low maternal education and gender		SSRI exposure Adjusted for BDI scores at assessment age, birth weight, low maternal education and gender		SSRI exposure Adjusted for STAI-T scores at assessment age, birth weight, low maternal education and gender	
	B (95% CI)	beta	B (95% CI)	beta	B (95% CI)	beta	B (95% CI)	beta	B (95% CI)	beta
BSID Cognition	**-0.9* (-1.5 to -0.3)**	**-0.28**	**-0.8* (-1.4 to -0.1)**	**-0.24**	-0.6 (-1.3 to 0.2)	-0.19	**-0.9* (-1.6 to -0.2)**	**-0.27**	-0.7 (-1.3 to 0.006)	-0.21
BSID Gross motor	**-1.1* (-2.1 to -0.2)**	**-0.23**	**-1.1* (-2.1 to -0.04)**	**-0.23**	-0.8 (-2.0 to 0.3)	-0.18	**-1.2* (-2.3 to -0.1)**	**-0.24**	-1.0 (-2.1 to 0.2)	-0.20

BSID, Bayley Scales of Infant and Toddler Development; CI, confidence interval; BDI, Beck Depression Inventory; STAI-T, State Trait Anxiety Inventory-Trait
Multiple regression models all performed using method Enter.
Bold font signifies statistical significant differences.
* $P \leq 0.05$, two-tailed.

maternal mental state [19].

Nulman et al. [20] evaluated children's intelligence and behavioral outcomes measured once between the ages of 3 and 7 years. The IQs of the children who had been exposed to SSRI or venlafaxine prenatally were significantly lower than those of the children not exposed to SSRI and whose mothers did not suffer from depression. They were unable to differentiate between the effects of medication or maternal depression during pregnancy on children's FSIQs. The results of the study by Nulman et al. [20] are similar to ours and largely in line with our data. In addition, we meticulously adjusted our analyses for maternal mental state, including both depression and anxiety, and its severity.

In the univariate analyses, gross motor development in our study was related to SSRI exposure only, not to maternal mental state in pregnancy or at the age of assessment. This is consistent with other studies that showed poorer gross motor function after antenatal SSRI exposure [18,21,23]. In our study, severity of anxiety was the only factor altering the significance of the relation between SSRI exposure and gross motor scores.

We did not find differences in fine motor outcome between SSRI-exposed children and non-SSRI exposed children. Pedersen et al. also did not find differences in fine motor skills [21]. One hypothesis to explain this finding concerns the differential effects of SSRIs on different areas or networks in the brain, which may depend on the developmental stage of that particular network [12]. Another hypothesis is that the BSID test is not sensitive enough to detect subtle fine motor differences at this young age.

We did not find behavioral differences that could be ascribed to SSRI exposure. Behavioral outcome was associated with maternal psychopathology at assessment age. Recently, internalizing and externalizing problems according to the CBCL were reported to be increased in children aged 5 to 6 years after prenatal exposure to SSRIs [33]. Associations between prenatal SSRI exposure and symptoms of pervasive developmental disorder PDD and autism spectrum disorder ASD have also been investigated in several other studies, but results are conflicting [17,25,34]. Possibly behavioral and emotional consequences of prenatal SSRI exposure may only become apparent at a later age, and not already at 2.5 years.

Our study has several strengths. First, our cohort has an adequate group size that enabled us to control for maternal psychopathology and its severity. Our non-SSRI group might not be the ideal comparison group, because it may have a greater range of distribution in outcome than expected in a normal population, due to more maternal mental psychopathology. Still, using this comparison group, we were able to disentangle the effect of maternal psychopathology and that of maternal use of SSRI on outcome of the children. Second, our study has a prospective design, thus including women before delivery to avoid selection bias after delivery, as parents might be more interested in developmental follow-up if their child encountered problems during or after birth. Third, the women's general background characteristics were quite similar in both groups. Fourth, we used a population of pregnant women not needing tertiary care. Therefore the mother-child pairs were not contaminated with confounders such as perinatal infection, prematurity, low Apgar score, or extremely low birth weight. Fifth, we had very few missing data and an excellent follow-up rate.

We also recognize some limitations to our study. First, our inclusion was open, and we did not perform a randomized controlled trial. The latter is the preferred way of studying differences in outcome between groups. Obviously, decisions regarding SSRI prescription during pregnancy will be arrived at by joint agreement between the pregnant women and their doctors and will depend on the severity of the mothers' mental problems. This excluded the possibility of performing a randomized controlled trial. Second, maternal depression and anxiety were assessed using questionnaires rather than a structured psychiatric interview, the latter being the best procedure for diagnosing depression

and anxiety. Nevertheless, it resembles clinical practice in the Netherlands where antidepressant drugs are mostly prescribed by general practitioners. This may have led to a slight overestimation rather than underestimation of the incidence of depression and anxiety, which in turn may have diluted the results. Third, different SSRIs have different potencies for monoamine and other neurotransmitter transporters and may have different effects on brain development in utero [9]. Due to the group size we were not able to differentiate effects between the various SSRIs, but separate analyses showed no differences in outcome between children exposed to paroxetine or one of the other SSRIs. Therefore we believe that our results can be generalized to all SSRIs.

The scores on cognition and gross motor outcome of the SSRI-exposed group fall within the normal range. This may lead to the conclusion that the negative effects might not be clinically relevant, but we believe otherwise. If the normal curve of outcome shifts to the left, and if this is persistent over time, then the overall performance of the whole group becomes poorer. In a population in which 2% to 8% of pregnant women are taking an SSRI, differences of one-third of the SD may have considerable long-term consequences for the offspring, such as school performance and income.

Our findings may have implications. SSRI exposure during pregnancy has a substantial, long-term negative influence on cognitive and gross motor development of the child. Whether this effect is irreversible is unknown. Animal studies have reported that neuronal networks of rats exposed to SSRIs in utero are permanently changed. These rats behave differently in adult life [11]. Recently different reports revealed altered brain development and connectivity patterns in human neonates [14,15]. This indicates that altered neurodevelopment following prenatal SSRI-exposure in humans is conceivable, but may become apparent only at later age. These are strong arguments against taking SSRIs for maternal depression or anxiety during pregnancy. Conversely, cognitive development of the child is negatively associated with maternal psychopathology during pregnancy and at the age of testing. To prevent the child's cognitive development from being disturbed, it may be necessary for the mother to use medication. Of note, despite SSRI treatment, 40% of the women in our study group remained depressed and/or suffered anxiety. This raises questions about the effectiveness of medical treatment and calls for alternatives. Reportedly, cognitive behavior therapy (CBT) and pharmacotherapy are equally effective in the treatment of depression [35]. During pregnancy CBT may be a better alternative for the child. Given the current high rate of SSRIs prescribed to pregnant women, this suggestion may have considerable consequences for public health.

5. Conclusion

SSRI exposure during pregnancy is associated with poorer cognitive and gross motor development of the child at age 2.5 years. Physicians should be aware that during pregnancy SSRIs should be prescribed cautiously by all professionals involved, keeping in mind that non-treatment of depression in pregnant women could also lead to substantial negative outcomes in the offspring.

CRediT authorship contribution statement

Christine N. van der Veere:Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing - original draft, Writing - review & editing.**Nathalie K.S. de Vries**:Conceptualization, Data curation, Resources.**Koenraad N.J.A. Van Braeckel**: Conceptualization, Investigation.**Arend F. Bos**:Methodology, Resources, Supervision, Validation, Visualization.

Declaration of competing interest

None.

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