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Attention-deficit/hyperactivity disorder in children following prenatal exposure to antidepressants: results from the Norwegian mother, father and child cohort study

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Objective To determine the association between child attention-deficit/hyperactivity disorder (ADHD) and prenatal exposure to selective serotonin (SSRI) and serotonin-norepinephrine (SNRI) reuptake inhibitor antidepressants, by timing and duration, with quantification of bias due to exposure misclassification.

Design Norwegian Mother, Father and Child Cohort Study and national health registries.

Setting Nationwide, Norway.

Population A total of 6395 children born to women who reported depression/anxiety in pregnancy and were either medicated with SSRI/SNRI in pregnancy (n = 818) or non-medicated (n = 5228), or did not report depression/anxiety but used antidepressants 6 months before pregnancy (discontinuers, n = 349).

Main outcome measure Diagnosis of ADHD or filled prescription for ADHD medication in children, and mother-reported symptoms of ADHD by child age 5 years.

Results When the hazard was averaged over the duration of the study follow up, there was no difference in ADHD risk between ever in utero SSRI/SNRI-exposed children and comparators (weighted hazard ratio [wHR] 1.07, 95% CI 0.76–1.51 versus non-medicated; wHR 1.53, 95% CI 0.77–3.07 versus discontinuers). Underestimation of effects due to exposure misclassification was modest. In early childhood, the risk for ADHD was lower with prenatal SSRI/SNRI exposure compared with no exposure, and so were ADHD symptoms (weighted β −0.23, 95% CI −0.39 to −0.08); this risk became elevated at child age 7–9 years (wHR 1.93, 95% CI 1.22–3.05). Maternal depression/anxiety before pregnancy was independently associated with child ADHD.

Conclusion Prenatal SSRI/SNRI exposure is unlikely to considerably increase the risk of child ADHD beyond that posed by maternal depression/anxiety. The elevated risk at child age 7–9 years needs to be elucidated.

Keywords Epidemiology: paediatric, epidemiology: perinatal, psychiatry.

Tweetable abstract Women with depression who use antidepressants in pregnancy do not have greater risk of having children with ADHD. Findings in school-age children needs follow up.

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Introduction

Pregnant women may at times need antidepressants to treat mental disorders. Selective serotonin reuptake inhibitors (SSRIs) are the preferred therapeutic choice in this population, and they are taken by 1–5% of pregnant women in Europe and up to 8% in the USA;[1–3] other antidepressants, such as serotonin-norepinephrine reuptake inhibitors

(SNRIs), are less often used (<1%).[2] Perinatal antidepressant exposure alters offspring behaviour and brain structure in animal research, possibly through serotonin dysregulation.[4,5] Risk for attention-deficit/hyperactivity disorder (ADHD) has therefore been investigated in human pregnancy, but findings are inconsistent.[5–7]

Results of one meta-analysis has suggested a moderate increased risk for ADHD in children prenatally exposed to antidepressants relative to unexposed (risk ratio 1.39, 95% CI 1.21–1.61),[6] but the association decreased to the null in sibling-matched analyses.[5] Even though familial factors are presumed to largely explain the increased ADHD risk in ever exposed children, whether timing of prenatal antidepressant exposure, and so duration, confer different ADHD risks remains unresolved.[5,8]

Quantifying risks for child behavioural disorders from both a diagnostic and a symptom perspective is also critical,[7] as an additional 5% of children beyond the 2–7% having a diagnosis display symptoms of ADHD that do not meet fully the diagnostic criteria.[9] Given the burden, consequences and unclear aetiology of ADHD in children,[9] a more conclusive understanding of the risk posed by intrauterine antidepressant exposure is needed.[7]

This study sought to fill these knowledge gaps by quantifying the association of child ADHD, measured both as diagnoses and symptoms, with prenatal SSRI/SNRI antidepressant exposure defined as ever in pregnancy, at different timings or durations. To address possible bias by exposure misclassification, we replicated the main analysis for ever exposure to SSRI/SNRI in a sub-population of women who both self-reported and filled prescriptions for antidepressants.

Methods

Study population and data collection

This study is based on the Norwegian Mother, Father and Child Cohort Study (MoBa),[10,11] linked to records in the Medical Birth Registry of Norway,[12] the Norwegian Prescription Database (NorPD),[13] and the Norwegian Patient Registry (NPR)[14] via the maternal personal identification number. MoBa is a nationwide, prospective population-based pregnancy study conducted by the Norwegian Institute of Public Health.[10,11] Participants were recruited in 1999–2008 through a postal invitation in connection with a publicly offered routine ultrasound at 17–18 weeks of gestation. Prenatal data were gathered via two self-administered questionnaires at week 17 (Q1) and week 30 (Q3). Postnatal follow-up questionnaires on maternal and child health were sent to mothers from child age 6 months to adolescence. Follow up of children started in 1999 and is still ongoing. Prospective fathers also completed one prenatal questionnaire at week 17. The current study is based on version 9 of the quality-assured data files released for research. The cohort now includes 114 500 children, 95 200 mothers and 77 300 fathers.[10] The participation rate for all invited pregnancies was 41%.[11] This study followed the STROBE reporting guideline for cohort studies.

The Medical Birth Registry of Norway is a nationwide registry based on compulsory notification of all live births, stillbirths and induced abortions.[12] The NorPD collects data on all prescribed medications dispensed from community pharmacies irrespective of reimbursement since 2004. The NPR contains records on admission to hospitals and specialist health care since 2008. The data include dates of admission and discharge, primary and secondary diagnoses, and cover all government-owned hospitals and outpatient clinics, and all private health clinics that receive governmental reimbursement. Diagnostic codes in the NPR follow the International Classification of Diseases, version 10 (ICD-10). Figure 1 outlines the exclusion criteria to achieve the final ADHD diagnosis sample, with complete registry-based outcome data for all MoBa children, and the final ADHD symptom sample, including MoBa children with maternally reported data at age 5 years.

Self-reported clinical depression and anxiety

To emulate the design of a hypothetical randomised clinical trial using observational data, we included pregnancies among women reporting depression and/or anxiety during gestation.[15,16] In Q1 and Q3 women were presented with a list of concurrent illnesses, and could report whether they were having 'depression' or 'anxiety' or 'other mental disorders' (hereafter, clinical depression/anxiety) in pregnancy, and likewise in the time before pregnancy. We additionally included women (discontinuers) with no self-reported clinical depression/anxiety in pregnancy, but who reported using antidepressants solely in the 6 months before pregnancy.

The study measured severity of maternal symptoms of depression and anxiety at weeks 17 and 30 using the short versions of The Hopkins Symptom Checklist-25, i.e. the 5-item (SCL-5) scale.[17,18] More information is outlined in the Appendix S1: Supplementary methods.

SSRI and SNRI exposure

In Q1 and Q3 women reported the name of the medication taken and timing of use in 4-week intervals according to indication (Q1 for week 0–13+ and also 6 months before pregnancy; Q3 for week 13–29+).[19] Drug classification was based on the Anatomical Therapeutic Chemical (ATC) Classification System.[20]

In a sub-sample of women enrolled in MoBa since 2004, NorPD was used as a complementary source of exposure data. The NorPD includes ATC codes of individual antidepressants dispensed, dispensing dates and the amount dispensed. We measured any antidepressant prescriptions filled within the period from pregnancy start to

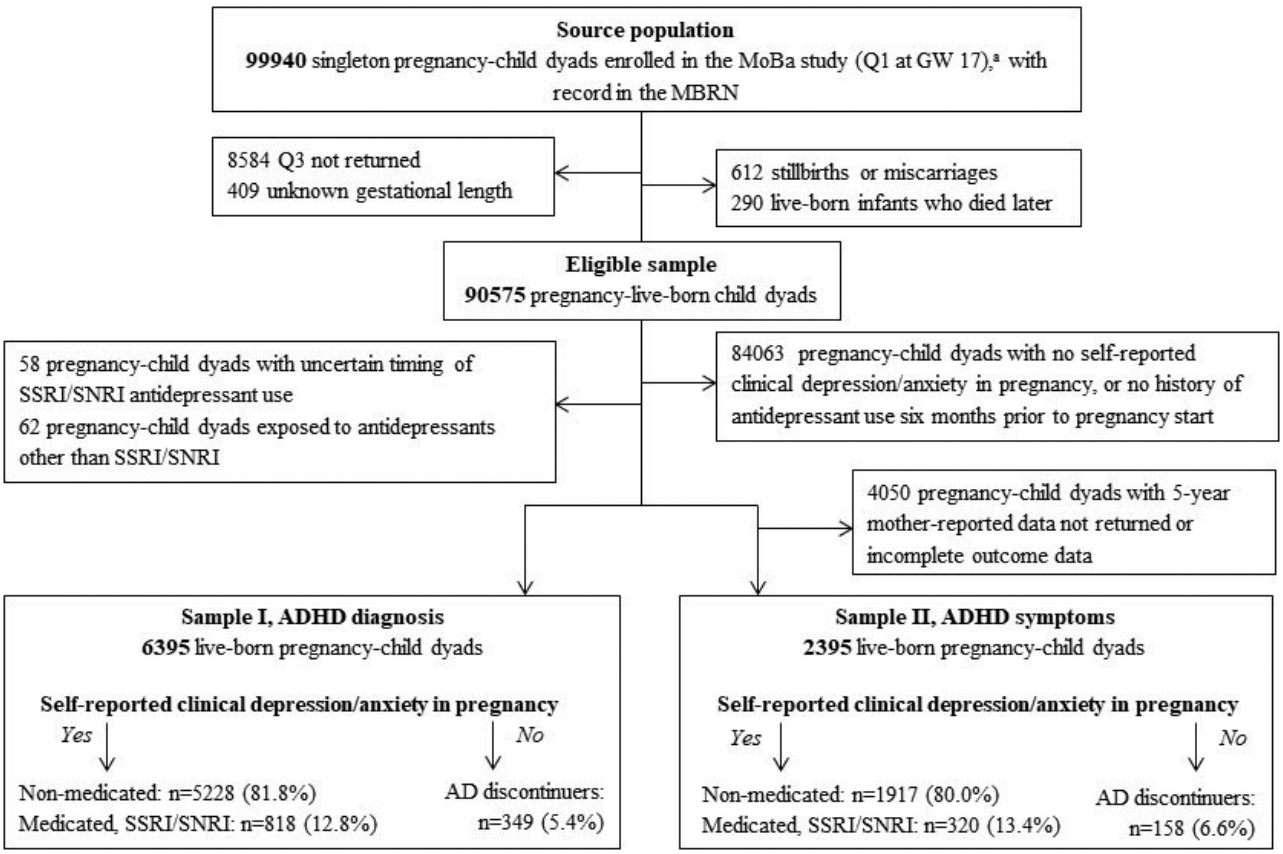

Figure 1. Flow-chart to achieve final study samples. §Conditions of exclusion may overlap. AD, antidepressant; ADHD, attention-deficit/hyperactivity disorder; GW, gestational week; MBRN, Medical Birth Registry of Norway; MoBa, Norwegian Mother, Father and Child Cohort Study; Q1, questionnaire 1 in MoBa; Q3, questionnaire 3 in MoBa; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors. aQ1 is the first MoBa questionnaire completed at gestational week 17; its completion implies enrolment into the study. About 10 000 pregnancies with an MBRN record did not complete Q1.

delivery[21] (see Appendix S1: Supplementary methods for additional detail).

Gestational exposure to each individual antidepressant was defined as exposure to a drug belonging to the ATC group N06A. SSRIs (sertraline, fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine) and SNRIs (venlafaxine, duloxetine) were grouped together (SSRI/SNRI).

Because symptoms of depression/anxiety were measured at weeks 17 and 30, and reflected disease severity in the previous 2 weeks, we defined the following points of exposure in the timing analysis:[8,22] early (weeks 1–16), mid (weeks 17–28) and late (week 29 and beyond) pregnancy. Duration of SSRI/SNRI use was defined according to how many 4-week intervals, out of the eight possible throughout pregnancy, were checked. These were grouped into '1–8 weeks', '9–20 weeks' or '>20 weeks'. In addition, we defined an ever exposure group during gestation. Women were classified as exposed if they reported use of SSRI/SNRI during these periods. Two mutually exclusive comparison groups were defined: (1) Non-medicated – women with self-reported clinical depression/anxiety in pregnancy but non-medicated; (2) Discontinuers – women who reported use of any antidepressant only in the 6-month period before pregnancy, who did not report depression/anxiety in pregnancy.

ADHD diagnosis

A diagnosis of ADHD in the offspring (hereafter, ADHD) was defined as (1) at least one primary or secondary diagnosis by a specialist in the Norwegian healthcare system, as registered in the NPR (ICD-10 codes F90: hyperkinetic disorder), in the period 2008–2015; or (2) one or more dispensed ADHD medications licensed in Norway (i.e. methylphenidate, atomoxetine, racemic amphetamine, dexamphetamine and lisdexamphetamine) in NorPD between 2004 and 2016.[23] The ICD-10 codes diagnosis of hyperkinetic disorder requires the combination of both inattentive and hyperactive symptoms.[24] The majority of MoBa children were born in 2004 or later, so outcome data since

birth were available for most of the children in this study (Figure S1).

ADHD symptoms

Child ADHD symptoms by age 5 years were mother-reported via completion of the widely used, validated Conners Parent Rating Scale-Revised (CPRS-R).[25] MoBa included 12 CPRS-R items measuring the 'inattention' and 'hyperactivity/impulsivity' domains. Mothers were asked to rate whether each item reflected their child's behaviour in the last 6 months. The CPRS-R items and related scoring have been previously published.[22] Mean CPRS-R score was calculated and standardised; higher *z*-scores indicated greater ADHD symptoms. In the current study, the internal CPRS-R consistency was 0.90.

Measured confounders

We identified a sufficient set of confounders with the aid of directed acyclic graphs.[26] These were pre-pregnancy maternal body mass index, parity, education and gross yearly income, marital status, folic acid, smoking and alcohol use in early pregnancy, paternal age, and an obstetric comorbidity index including maternal age, illicit substance use and other factors[27] (see Appendix S1: Supplementary Methods); co-medication in early pregnancy with opioid analgesics, paracetamol, nonsteroidal anti-inflammatory drugs, benzodiazepine/z-hypnotics, and antipsychotics; and severity of maternal depressive and anxiety symptoms in pregnancy via the SCL-5, and Life Time History of Major Depression.[28] We included maternal and paternal filled prescriptions for ADHD medication at any time as proxy of familial risk of ADHD. In separate models, we included other maternal, paternal and child factors (Appendix S1: Supplementary methods and Table S1).

Data analysis

To estimate associations with SSRI/SNRI exposure as ever in gestation and by duration, we fitted unadjusted and weighted analyses using inverse probability of treatment weighting, based on the propensity score.[29] Logistic regression models were first fitted to estimate the probability of 'SSRI/SNRI exposure' as ever and in the duration windows (1–8, 9–20, >20 weeks), relative to non-medicated or discontinuers, given the set of confounders. To estimate associations by timing of exposure, we fitted marginal structural models[30] with two time-points to account for time-varying SSRI/SNRI exposure and time-varying confounders (i.e. SCL-5 in pregnancy and co-medications), which are affected by previous SSRI/SNRI treatment, as illustrated previously.[8,22] We estimated the probability of SSRI/SNRI treatment using a pooled logistic regression in which the outcome was current treatment with an SSRI/SNRI in mid or late pregnancy, and covariates were maternal baseline, time-varying and time-fixed confounders, and SSRI/SNRI in early pregnancy. We then derived stabilised inverse probability of treatment weighting for each pregnancy at each time-point.

To estimate standardised mean differences in symptoms and hazard ratio for ADHD, we respectively fitted unadjusted and weighted generalised linear and Cox regression models with robust standard errors. In the Cox regressions, we used child age as time scale and a quadratic term for year of birth; the follow-up period for all live-born children started at birth and ended on the date of ADHD diagnosis, date of first drug prescription for ADHD, or 31 December 2016, whichever came first. The current study did not have information about dates of potential emigration or death, but only whether these events had occurred – 91 (1.4%) children had emigrated. Because the proportionality hazard assumption was not met, we split the follow-up time at child age 7 and 9 years, estimating period-specific hazard ratios. The splitting points were selected based on the weighted failure curves and age-specific incidence rates (Figures S2, Table S2). All statistical analyses were performed using Stata MP 16. Data are presented as unadjusted and weighted hazard ratios (wHR), and as standardised means scores with 95% CI. Power analysis is outlined in Table S3.

To address possible bias by exposure misclassification, we replicated the main analyses for SSRI/SNRI ever exposure in a sub-sample of women enrolled in MoBa since 2004, and compared 'truly SSRI/SNRI-exposed' with 'truly unexposed' pregnancies, based on concordant exposure information from two sources. To document confounding by maternal pre-existing depression/anxiety, we estimated the independent association of this factor with child ADHD, and further adjusted the weighted effect estimates for SSRI/SNRI exposure by this covariate. To assess the robustness of the findings, we carried out additional sub-group and sensitivity analyses, as described in detail in Appendix S1: Supplementary methods. Up to 16.5% of the pregnancies had missing values in at least one of the sufficient confounders. Under the assumption that data were missing at random, we imputed incomplete data via multiple imputation with chained equation (ten replications)[31–33] (see Appendix S1: Supplementary methods for additional detail).

Patient and public involvement

We did not include patient and public directly throughout the research process (formulation of research questions, outcome measures development, study design, recruitment, the conduct of the study, and dissemination of the results).

Results

The study included 6395 live-born pregnancy–child dyads with data on child ADHD (sample I); of these, 2395 had

available mother-reported data on ADHD symptoms by child age 5 years (sample II) (Figure 1). Few women (2.5–3.2%) participated with more than one pregnancy in both samples. Prenatal SSRI/SNRI exposure was reported by 818 pregnant women in sample I, and 320 in sample II, mainly for the indication of depression and/or anxiety (96.5%), and as monotherapy (96.3%). The indication for use of antidepressants 6 months before pregnancy was unknown for most discontinuers, and only 36.4% reported pre-existing depression/anxiety. Baseline characteristics of the samples are shown in Table 1 and Table S4.

Associations with child ADHD

Overall, 323 (5.1%) children had ADHD. The incidence rate was highest at age 7–10 years (Figures S2–S3, Table S2), and in boys. The mean follow-up time was similar across the exposure groups (mean range 10.7–10.9 years, standard deviation 2.2 for all groups).

After weighting, the averaged hazard for ADHD reduced substantially in SSRI/SNRI ever in-utero exposed children compared with children born to non-medicated women (wHR 1.07, 95% CI 0.76–1.51), but it remained elevated in children born to discontinuers (wHR 1.53, 95% CI 0.77–3.07). There was satisfactory balance of covariates between the exposure groups after weighting (Figure S4).

There was no association between SSRI/SNRI exposure in mid or late pregnancy and child ADHD, relative to both comparators (Table 2), albeit the estimated 95% CI were imprecise. In the duration analysis, the ADHD hazard was of smaller magnitude for SSRI/SNRI exposure in 1–8 weeks (7–50% increased hazard) relative to 9–20 weeks (40–113% increased hazard). There was no clear duration–response relationship (Table 2).

Temporal associations with child ADHD

As shown in Figure 2, the period-specific hazards indicate that in pre- and early school-age, the ADHD risk was lower in children ever exposed to SSRI/SNRI compared with those born to non-medicated women (wHR 0.31, 95% CI 0.13–0.76). In the age band 7–9 years, this risk was elevated among exposed relative to both comparators (wHR 1.93, 95% CI 1.22–3.05; wHR 2.59, 95% CI 0.94–7.12).

Associations with child ADHD symptoms

Children of mothers who ever used SSRI/SNRI in pregnancy had a lower small risk of ADHD symptoms at age 5 years compared with those born to non-medicated women (weighted β −0.23, 95% CI −0.39 to −0.08) or discontinuers (weighted β −0.18, 95% CI −0.45 to 0.09) (Table 2). There was no difference in ADHD symptoms between groups according to longer exposure duration.

Subgroup analyses and sensitivity analyses

The point estimates for ADHD with true SSRI/SNRI exposure were slightly larger (about 10%) than the main results; for ADHD symptoms the results were almost identical (Table S5).

Further adjustment for pre-existing clinical depression/anxiety attenuated the observed associations in the age band 7–9 years (Table S6), and this factor was independently associated with child ADHD (weighted, adjusted HR 1.34, 95% CI 1.05–1.72). Results of other sensitivity analyses did not deviate from the main analysis (Appendix S2: Supplementary results and Tables S7).

Discussion

Main findings

This study reports no substantial risk for ADHD with prenatal SSRI/SNRI antidepressant exposure at different timings during pregnancy, and no definite duration–response associations when the hazard of ADHD is averaged over the study's follow up. Misclassification of exposure could have underestimated by about 10% the observed point estimates, leading to an unaltered inference. When splitting the follow-up time, children prenatally exposed to SSRI/SNRI have lower risk for ADHD diagnosis and symptoms than unexposed children at preschool age. At age 7–9 years, prenatal SSRI/SNRI exposure was associated with greater ADHD risk in offspring, and this seemed to be mainly driven by longer duration of SSRI/SNRI exposure. After taking into account biases and confounding, our best estimate for the weighted hazard ratio was around 1.58–1.93 for ever in utero exposure to SSRI/SNRI, and 2.22–2.76 for 9–20 weeks duration. Nevertheless, we also document that maternal depression/anxiety, both during and before pregnancy, are possibly key factors of joined confounding, yielding substantial risk attenuation to the effect estimates for SSRI/SNRI in utero exposure.

Strengths and limitations

One strength is that we quantified the impact of exposure misclassification, applied methods to deal with time-varying exposure, confounders and missing data, and examined ADHD risks from a diagnosis and symptom perspective.[7] We attempted to limit confounding by indication by including only women with clinical depression/anxiety during pregnancy, and measured their symptom severity at two time-points in pregnancy using a validated instrument.[17] We carried out several sensitivity and subanalyses to explore the robustness of our findings; however, we cannot rule out the role of residual confounding by depression severity, use of teratogenic drugs, genetic, environmental or familial factors, or even chance, on our findings.

Table 1. Characteristics of sample I by prenatal SSRI/SNRI antidepressant exposure (N = 6395)

	Self-reported clinical depression/anxiety during pregnancy		
	Yes		No
	Non-medicated	Medicated SSRI/SNRI	AD discontinuers
Characteristics	*n* = 5228	*n* = 818	*n* = 349
Age (y); mean ± SD	29.6 ± 5.1	30.1 ± 5.1	29.7 ± 4.7
BMI at conception; mean ± SD	24.2 ± 4.5	24.5 ± 4.9	24.8 ± 4.9
Primiparity; *n* (%)	2892 (55.3)	384 (49.9)	167 (47.9)
Married/Cohabiting; *n* (%)	4775 (91.3)	716 (87.5)	318 (91.1)
Educational level;[a] *n* (%)			
University/College	2653 (50.8)	418 (51.1)	184 (52.7)
Lower than University/College	2541 (48.6)	399 (48.8)	163 (46.7)
Gross yearly income;[b] *n* (%)			
Average	3212 (61.4)	502 (61.4)	213 (61.0)
Low	1412 (27.0)	237 (29.0)	97 (27.8)
High	402 (7.7)	56 (6.9)	32 (9.2)
Smoking at week 17;[c] *n* (%)			
Yes	738 (14.1)	180 (22.0)	59 (16.9)
Stopped in pregnancy	1085 (20.8)	176 (21.5)	59 (16.9)
Alcohol use at week 17; *n* (%)			
No/very limited	4352 (83.2)	692 (84.6)	294 (84.2)
Medium/weekly use	154 (3.0)	24 (2.9)	9 (2.6)
Periconceptional folate use (yes); *n* (%)	4049 (77.5)	655 (80.1)	293 (84.0)
LTH of MD (yes);[d] *n* (%)	999 (19.1)	375 (45.8)	102 (29.2)
Pre-existing depression/anxiety (yes); *n* (%)	1905 (36.4)	766 (93.6)	286 (82.0)
Number of psychiatric disorders in pregnancy; *n* (%)[c]			
Two	649 (12.4)	195 (23.8)	–
Three	100 (1.9)	72 (8.8)	–
Depressive/anxiety symptoms; mean score ± SD			
SCL-5 at GW 17	1.8 ± 0.6	1.9 ± 0.7	1.5 ± 0.5
SCL-5 at GW 30	1.8 ± 0.6	1.8 ± 0.7	1.5 ± 0.5
Comorbidity index; mean ± SD	0.6 ± 1.0	0.6 ± 1.1	0.6 ± 1.1
Number of infections in pregnancy; mean ± SD	0.5 ± 0.8	0.5 ± 0.8	0.5 ± 0.7
Co-medication in early pregnancy (yes); *n* (%)			
Benzodiazepines/z-hypnotics	135 (2.6)	87 (10.6)	11 (3.2)
NSAIDs	400 (7.7)	85 (10.4)	30 (8.6)
Paracetamol	2675 (51.2)	431 (52.7)	191 (54.7)
Opioid analgesics	161 (3.1)	39 (4.8)	15 (4.3)
Antipsychotics	82 (1.6)	33 (4.0)	8 (2.3)
Antiepileptics	36 (0.7)	19 (2.3)	1 (0.3)
Illicit substance (yes);[e] *n* (%)	118 (2.3)	31 (3.8)	8 (2.3)
ADHD prescriptions;[f] *n* (%)	149 (2.9)	53 (6.5)	15 (4.3)

AD, antidepressant; ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; GW, gestational week; LTH of MD, life time history of major depression; NSAID, non-steroidal anti-inflammatory drugs; SCL-5, short version (5-item) of The Hopkins Symptom Checklist; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor.

Numbers may not add up to total due to missing values: education (0.6%), smoking (1.2%), BMI at conception (3.2%), LTH of MD (3.0%), income (3.6%) and alcohol use (13.6%). For the SCL-5, missing values were 5.6% and 3.7% in early and late pregnancy, respectively.

[a]Includes ongoing or completed educational level.

[b]Average indicates income approximately between US$ 17 501 and US$ 46 800; Low indicates income ≤US$ 17 500; High indicates income ≥US $ 46 801.

[c]The remaining proportion were non-smokers or had a single disorder.

[d]Defined as Kendlers Life-time major depression scale score of three or more simultaneous depressive symptoms of duration of more than 2 weeks.

[e]Indicates use before and/or during early pregnancy.

[f]Indicates prescription for any ADHD medication filled by mothers at any time.

Table 2. Associations of SSRI/SNRI windows of exposure with child ADHD (sample I) and symptoms at age 5 years (sample II)

Exposure window	No.	No. events	IR per 1000 py	SSRI/SNRI versus Non-medicated		SSRI/SNRI versus AD discontinuers	
				Sample I, ADHD diagnosis			
				Unadjusted HR (95% CI)	Weighted* HR (95% CI)	Unadjusted HR (95% CI)	Weighted* HR (95% CI)
Non-medicated	5228	250	4.4	Reference	Reference		
AD discontinuers	349	14	3.8	—	—	Reference	Reference
SSRI/SNRI, ever	818	54	6.2	1.42 (1.06–1.91)	1.07 (0.76–1.51)	1.64 (0.91–2.96)	1.53 (0.77–3.07)
By duration in pregnancy**							
SSRI/SNRI, 1–8 weeks	432	27	5.8	1.32 (0.89–1.95)	1.07 (0.64–1.77)	1.53 (0.81–2.90)	1.50 (0.74–3.05)
SSRI/SNRI, 9–20 weeks	193	18	8.8	2.05 (1.26–3.31)	1.40 (0.79–2.50)	2.37 (1.19–4.74)	2.13 (0.97–4.68)
SSRI/SNRI, >20 weeks	193	9	4.4	1.04 (0.53–2.03)	0.85 (0.33–2.18)	1.16 (0.50–2.67)	0.89 (0.38–2.12)
By timing in pregnancy***							
SSRI/SNRI, mid-pregnancy	302	18	5.6	1.25 (0.77–2.01)	0.98 (0.55–1.71)	1.05 (0.61–1.80)	0.82 (0.45–1.52)
SSRI/SNRI, late pregnancy	252	15	5.6	1.24 (0.74–2.09)	1.08 (0.47–2.47)	1.04 (0.59–1.85)	0.97 (0.43–2.19)
	No.	**Mean**	**SD**				
				Sample II, ADHD symptoms			
				Unadjusted β (95% CI)	Weighted* β (95% CI)	Unadjusted β (95% CI)	Weighted* β (95% CI)
Non-medicated	1917	1.50	0.49	Reference	Reference	—	—
AD discontinuers	158	1.45	0.42	—	—	Reference	Reference
SSRI/SNRI, ever	320	1.47	0.43	−0.09 (−0.22, 0.04)	−0.23 (−0.39, −0.08)	0.03 (−0.18, 0.24)	−0.18 (−0.45, 0.09)
By duration in pregnancy**							
SSRI/SNRI, 1–8 weeks	158	1.45	0.41	−0.14 (−0.31, 0.04)	−0.27 (−0.46, −0.08)	−0.02 (−0.26, 0.22)	−0.17 (−0.43, 0.10)
SSRI/SNRI, 9–20 weeks	75	1.47	0.47	−0.09 (−0.37, 0.19)	−0.29 (−0.56, −0.02)	0.03 (−0.29, 0.36)	−0.31 (−0.67, 0.05)
SSRI/SNRI, >20 weeks	87	1.50	0.43	−0.01 (−0.25, 0.23)	−0.07 (−0.44, 0.29)	0.12 (−0.17, 0.40)	−0.02 (−0.36, 0.32)
By timing in pregnancy***							
SSRI/SNRI, mid-pregnancy	119	1.52	0.46	0.05 (−0.17, 0.27)	−0.09 (−0.37, 0.19)	0.19 (−0.06, 0.43)	0.06 (−0.22, 0.34)
SSRI/SNRI, late pregnancy	100	1.52	0.46	0.06 (−0.18, 0.30)	−0.11 (−0.42, 0.21)	0.19 (−0.07, 0.45)	0.03 (−0.28, 0.35)

AD, antidepressant; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; HR, hazard ratio; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

β: indicates standardised mean difference in symptoms of ADHD, as parent reported via the Conners Parent Rating Scale revised version.

*Weighted with stabilised inverse probability of treatment weighting (constructed at each time-point using baseline covariates, time-varying and time-fixed confounding factors, and SSRI history treatment) in the timing analysis, and stabilised inverse probability of treatment weighting using same set of covariates by duration and by any time/any duration.

**The week intervals do not imply that women took the medication continuously in all the weeks; women could check in the questionnaire exposure in 4-week intervals, e.g. weeks 0–4, 5–8, and so on.

***The reference is unexposed women within the exposure window.

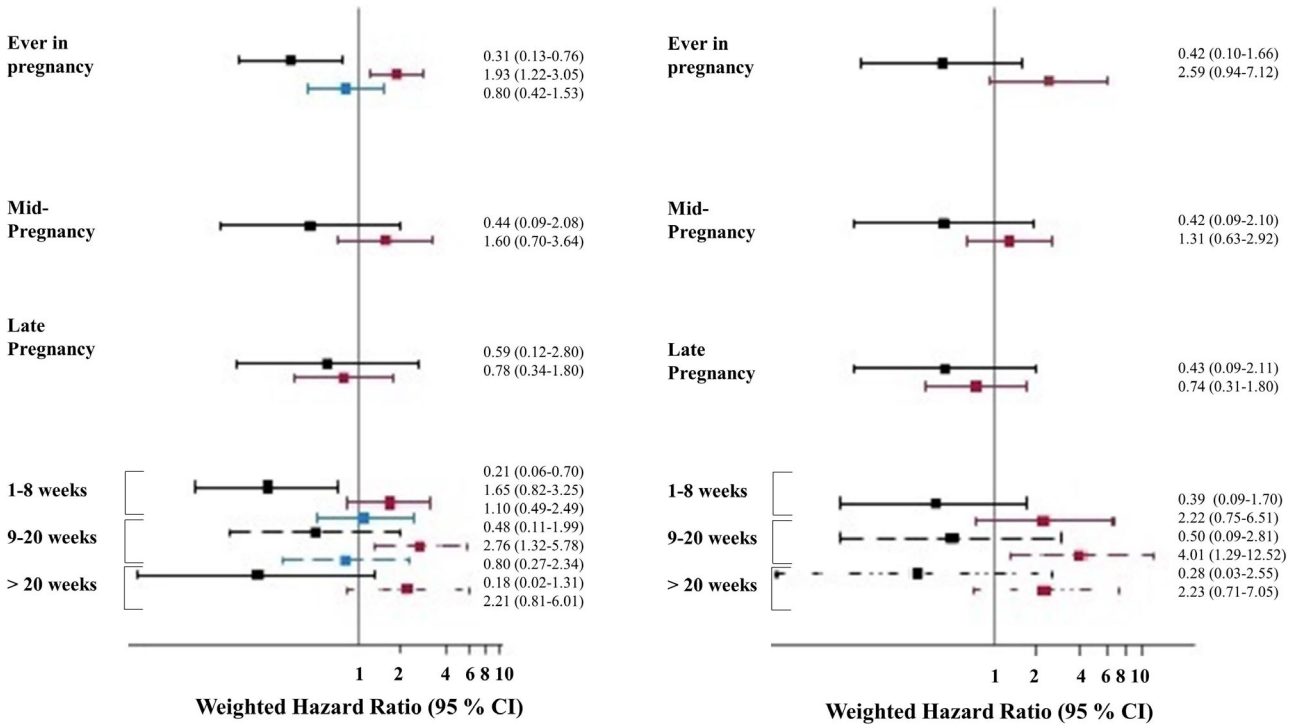

Figure 2. Period-specific associations of SSRI/SNRI windows of exposure with child ADHD. Point estimates <1 favours SSRI/SNRI exposure. Point estimates >1 favours reference exposure. For duration of exposure, the continuous line indicates duration of 1–8 weeks; the dashed line 9–20 weeks; and the dot-dot-dash line > 20 weeks. SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors. In the age band ≥ 9 years, no period-specific hazard ratio could be computed for the >20 weeks and timing windows in (A) and in all exposure windows in (B) because of few ADHD cases.

Several limitations need mentioning. Symptoms of depression and anxiety were not measured at baseline. We relied on maternal self-report of depression/anxiety during or before pregnancy, which cannot replace a clinical diagnosis. Information on dosage is not available in MoBa. Child ADHD symptoms were mother-reported, but the internal consistency of the CPRS-R was high. Although the risk of outcome misclassification cannot be ruled out, this was probably non-differential, and the depression-distortion bias had a negligible impact on our effect estimates. The MoBa study has a low response rate (41%), with a possible self-selection of the healthiest women into the cohort.[10,11] Although association measures have been shown to be valid in MoBa in relation to immediate birth outcomes,[34] the impact of selection bias on longer-term outcomes cannot be excluded.[35] Our small sample size precluded detection of small effect sizes, analyses of SSRI and SNRI as separate groups, or for individual antidepressants, as well as sibling-design analysis. We could, however, take into account familial risk of ADHD using parental use of ADHD medications, as well as parental self-report of ADHD symptoms in a subsample. The low number (m = 10) of multiple imputed data sets may have produced substantial variance between imputations.

Interpretation

In line with previous studies showing hazard ratios of 0.75–0.98[36,37] with 1.20 as the upper bound of the pooled 95% CI,[38] we found no substantial difference in ADHD risk between prenatally SSRI/SNRI exposed children and those born to non-medicated women. Albeit with some uncertainty, the averaged hazard for ADHD with SSRI/SNRI exposure at any time during pregnancy was moderately elevated when compared with children born to discontinuers, and likewise following 9–20 weeks of exposure duration. These contrasting results across comparisons may suggest that antenatal depression/anxiety is possibly a key confounder. Although confounding by indication was limited in the former comparison, by restriction, discontinuers had no active depression/anxiety in pregnancy.[16] This risk of confounding did not emerge when we fitted methods able to account for time-varying depression symptom severity in pregnancy.[30]

Causal interpretation of HR is risky, however, and effect estimates averaged over the duration of a study's follow up may not be informative.[39] In this study, the HRs changed over time and this was not due to a cohort effect or to sex-specific differences. We observed lower or at least equal

ADHD risk in SSRI/SNRI-exposed children compared with unexposed children in early childhood. Yet, an increased risk emerged in mid-childhood (7–9 years). This temporal trend was apparent across all the windows of exposure, except for SSRI/SNRI in late pregnancy, which partly aligns with the result of Boukhris et al.[40] Further comparison with previous research is difficult because adjusted survival curves are often not presented, the follow-up time is too short, or it is unclear whether the hazard ratios were constant over time.[36,39,41–43]

The observed ADHD risk reduction in early childhood aligns with our analysis by child age 5 years; nevertheless, the effect sizes were small and unlikely to reach clinical relevance. This absence of risk aligns with results of previous studies that controlled for maternal mood disorders, genetic liability or familial environment.[44] Alternative explanations are possible, including chance, few ADHD cases in early childhood, or distorted maternal report on child ADHD symptoms.[45]

The apparent elevated risk for ADHD observed in mid-childhood, at age 7–9 years, needs careful interpretation. We found some evidence for a moderate association between SSRI/SNRI ever exposure or for 9–20 weeks duration, relative to unexposed in this age band. Evidence was weak for longer duration of exposure, and there were no substantial timing associations. Inattention symptoms are more easily detected as children grow older.[46] Our age-specific results may then be explained by measurement issues, but bias due to small sample size, or competing risks cannot be ruled out. If the former explanation holds true, then the question remains as to why measurement bias would be differential across the exposure groups. It could be argued that children prenatally exposed to an active, non-medicated depression are more susceptible to the combined type of ADHD,[46] often detected in earlier childhood. This would reduce the number of susceptible children in this group over time, and in turn produce a fictitious increased hazard for the SSRI/SNRI-exposed.[39] At the same time, an age-specific association between prenatal SSRI/SNRI and predominantly inattentive ADHD subtype,[46] cannot be completely ruled out. The pathophysiology of ADHD involves multiple neuronal circuits, and serotonin has been shown to modulate the default mode network.[47,48] Yet, the role of age-specific genetic influences, or the importance of environmental exposure to depression or SSRI/SNRI on ADHD across ages, remains untestable in the current study.[49]

Conclusions

When the ADHD hazard was averaged over the duration of the study's follow-up, there was no association between timing or duration of prenatal SSRI/SNRI exposure and ADHD in offspring; exposure misclassification could have biased our results towards the null only modestly. The risk for child ADHD following prenatal SSRI/SNRI exposure was elevated only at age 7–9 years. The lack of a clear duration-related relationship and the observed confounding by maternal depression/anxiety in this study do not support a causal link between SSRI/SNRI and child ADHD. Research is needed on the age-specific associations between antidepressants in pregnancy and ADHD subtype trajectories.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

HN and MH conceived the study and applied for the study data. AL performed the data analysis, and MM contributed to data curation. AL wrote the initial draft. AL, MM, MH, HN, EY and TRK contributed to data interpretation and to writing the final manuscript. HN obtained funding. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Details of ethics approval

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data protection agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is based on regulations based on the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics on 26 March 2015 (reference number: 2015/442/REK Sør-Øst).

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Data availability statement

All relevant data are within the paper and its Supporting Information files. No additional data are available.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article. ■

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