Attention-Deficit/Hyperactivity Disorder in Children Following Prenatal Exposure to Antidepressants: results from the Norwegian Mother, Father and Child Cohort Study

Angela Lupattelli[1], Milada Mahic[2], Marte Handal[2], Eivind Ystrom[2], Ted Reichborn-Kjennerud[2], and Hedvig Nordeng[1]

[1]University of Oslo Faculty of Mathematics and Natural Sciences
[2]Norwegian Institute of Public Health

September 28, 2020

Abstract

Objective: To quantify the association between prenatal exposure to selective serotonin (SSRI) and serotonin-norepinephrine (SNRI) reuptake inhibitor antidepressants and ADHD in offspring, with quantification of exposure misclassification bias. Design: Norwegian Mother, Father and Child Cohort Study (MoBa), linked to national health registries. Setting: Norway. Population: 6395 children born to women who self-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 six months prior to pregnancy (discontinuers, n=349). Main outcome measure: Diagnosis of ADHD or redeemed prescription for ADHD medication in children, and mother-reported symptoms of ADHD at child age five years. Results: When the hazard was averaged over the duration of the study's 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% Confidence Interval (CI): 0.76-1.51, vs. non-medicated; wHR: 1.53, 95% CI: 0.77-3.07, vs. discontinuers). Underestimation of effects due to exposure misclassification was modest. At early childhood, the risk for ADHD was lower with prenatal SSRI/SNRI exposure compared with non-medicated, and so were ADHD symptoms (weighted β: -0.23, 95% CI: -0.39, -0.08); this risk became elevated at child age 7-9 years (wHR: 1.93, 95% CI: 1.22-3.05). Maternal depression/anxiety prior to 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 the underlying psychiatric illness. The elevated risk at child age 7-9 years needs to be further elucidated.

INTRODUCTION

Perinatal 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 to up to 8% in the US;[1-3] other antidepressants, such as serotonin-norepinephrine reuptake inhibitors (SNRIs), are less often used (<1%).[2] Perinatal antidepressant exposure altered offspring behavior and brain structure in animal research, possibly via serotonin dysregulation.[4] Risk for attention-deficit/hyperactivity disorder (ADHD) has therefore been investigated in human pregnancy, but findings remain inconclusive.[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 (RR): 1.39, 95% Confidence Interval (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 behavioral disorders from both a diagnostic and symptom perspective is also critical,[7] since 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 etiology 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 as ever exposure in pregnancy and according to timing and duration. 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 redeemed 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 (MBRN), [12] the Norwegian Prescription Database (NorPD),[13] and the Norwegian Patient Registry (NPR)[14] via the maternal personal identification number and pregnancy sequence. MoBa is a nation-wide, 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 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 114500 children, 95200 mothers and 77300 fathers.[10] The participation rate for all invited pregnancies was 41%.[11] This study followed the STROBE reporting guideline for cohort studies.

The MBRN 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 healthcare since 2008. The data include date of admission and discharge, primary and secondary diagnosis, 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 S1 outlines the exclusion criteria to achieve the i) final ADHD diagnosis sample, with complete registry-based outcome data for all MoBa children, and the ii) final ADHD symptom sample, including MoBa children with maternal-reported data at age 5 years.

Self-reported clinical depression and anxiety

We included pregnancies within women reporting depression and/or anxiety during gestation.[15,16] In MoBa 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 prior to pregnancy. To further tease apart the role of underlying maternal psychiatric disease from that of drug treatment in pregnancy, we additionally included women (discontinuers) with no self-reported clinical depression/anxiety in pregnancy, but who reported using antidepressant solely in the six month period prior to pregnancy.

The study measured severity of maternal symptoms of depression and anxiety at week 17 and 30 via 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 Supplement.

SSRI and SNRI exposure

In MoBa Q1 and Q3 women reported the name of the medication taken and timing of use in four-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 complementary source of exposure data. Available data in NorPD include 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 delivery, in accordance to prior research.[21] More detail about exposure definition in NorPD is given in the Supplement.

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 of their pharmacological properties.

Because symptoms of depression/anxiety were measured at week 17 and 30, and reflected disease severity in the prior two weeks, we defined the following points of exposure in the timing analysis, as described in prior work:[8,22] early (weeks 1-16), mid (weeks 17-28) and late (> week 29) pregnancy. Length 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: i) Non-medicated: women with self-reported clinical depression/anxiety in pregnancy but non-medicated; ii) Discontinuers: women who reported use of any antidepressant only in the six months period prior to pregnancy, who did not report depression/anxiety in pregnancy.

ADHD diagnosis

A diagnosis of ADHD in the offspring (hereafter, ADHD) was defined as i) at least one primary or secondary diagnosis in the NPR based on the ICD-10 codes F90 (hyperkinetic disorder), in the period 2008-2015; or ii) one or more dispensed ADHD medication licensed in Norway (i.e., methylphenidate, atomoxetine, racemic amphetamine, dexamphetamine, and lisdexamphetamine) in NorPD between 2004-2016.[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 and thus outcome data since birth were available for most of the children in this study (Figure S2).

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 selected CPRS-R items measuring the 'inattention' and 'hyperactivity/impulsivity' domains. Mothers were asked to rate whether each item reflected their child's behavior in the last six months. The CPRS-R items and related scoring have been previously published.[22] Mean CPRS-R score was calculated and standardized, and higher z-scores indicated greater ADHD symptoms. In the current study the internal CPRS-R consistency was 0.90.

Measured confounders and other postnatal factors

We identified a sufficient set of confounders with the aid of directed acyclic graphs.[26] These were pre-pregnancy maternal Body Mass Index (BMI), parity, education and gross yearly income, marital status, folic acid, smoking and alcohol use in early pregnancy, paternal age, and an obstetric comorbidity index,[27] as described in detail in the Supplement; co-medication in early pregnancy with opioid analgesics, paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepine/z-hypnotics, and antipsychotics; severity of maternal depressive and anxiety symptoms in pregnancy via the SCL-5, and Life Time History of Major Depression (LTH of MD), as measured in Q1 via five key depressive symptoms closely corresponding to the DSM-III-R criteria for lifetime major depression.[28] We included maternal and paternal filled prescriptions for ADHD medication as proxy of familial risk of ADHD. In separate models, we included other maternal psychiatric, paternal, child and postnatal factors (see Supplement and Table S1). More details on covariates are given in the Supplement.

Data analysis

To estimate associations with ever SSRI/SNRI exposure as ever in gestation and by duration, we fit crude and weighted analyses using inverse probability of treatment weighting (IPTW), based on the propensity score.[29] Logistic regression models were first fit to estimate the probability of 'SSRI/SNRI exposure' as ever and in the duration windows (1-8, 9-20, more than 20 weeks), relative to non-medicated or discontinuers, given the set of sufficient confounders. To estimate associations by timing of exposure, we fit marginal structural models (MSM)[30] with two time points to account for i) time-varying SSRI/SNRI exposure; ii) time-varying confounders (i.e, SCL-5 in pregnancy and co-medications) which are affected by prior SSRI/SNRI treatment, as illustrated in prior work.[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 stabilized IPTW for each pregnancy at each time point.

To estimate standardized mean differences in symptoms and hazard ratio (HR) for ADHD, we respectively fit crude and weighted generalized 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 to address left-truncation for children born before 2004; 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 children (1.4%) had emigrated). Because the proportionality hazard assumption was not met, we split the follow-up time at child age 7 and 9 years (Figures S3-S4), estimating period-specific HRs. All statistical analyses were performed by using Stata MP 16. Data are presented crude and weighted hazard ratios (wHR), and as standardized means scores with 95% CI. Power analysis is outlined in Table S2.

Sub-group and sensitivity analyses

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 between self-reported and prescription dispensation data. To document confounding by maternal pre-existing psychiatric illness, 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 the Supplement.

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] More detail is provided in the Supplement.

RESULTS

The study included 6395 liveborn 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 S1). Few women (2.5-3.2%) participated with more than one pregnancy in both samples. The majority of women (80.0-81.8%) reported non-medicated clinical depression/anxiety during pregnancy, and 12.8-13.4% (n=818 in sample I, n=320 in sample II) were taking SSRI/SNRI prenatally, mainly as monotherapy. Of the SSRI/SNRI exposed, 789 (96.5%) reported such use for the indication of depression and/or anxiety, and 30 (3.7%) were on polytherapy with another antidepressant (mainly mirtazapine or a tricyclic antidepressant). Baseline maternal and paternal sociodemographic, life-style and health characteristics, as well as selected child correlates by ever use of SSRI/SNRI in pregnancy, are shown in Table 1 (sample I) and Table S3 (sample II).

Associations with child ADHD

Overall, 323 (5.1%) children had ADHD; the cumulative incidence is shown in Figures S3-S4. The incidence rate was highest at age 7-10 years, and in boys (Tables S4-S5). The mean follow-up time was similar across the exposure groups (SSRI/SNRI exposed: 10.7 years (sd: 2.2); non-medicated: 10.9 years (sd: 2.2); discontinuers: 10.7 years (sd: 2.2)).

After weighting, the averaged hazard for ADHD reduced substantially in SSRI/SNRI ever in-utero exposed compared with non-medicated (wHR: 1.07, 95% CI: 0.76-1.51), but remained elevated when discontinuers acted as comparator (wHR: 1.53, 95% CI: 0.77-3.07). There was satisfactory balance of covariates between ever SSRI/SNRI-exposed and unexposed (Figure S5) after weighting, and the weights had acceptable characteristics (Table S6).

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 analyses, 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 1, the period-specific hazards indicate that at pre- and early school-age, the ADHD risk was lower among ever SSRI/SNRI exposed compared with non-medicated (wHR: 0.31, 95% CI: 0.13-0.76). In the age band 7-9 years, this risk was elevated among the exposed relative to both non-medicated (wHR: 1.93, 95% CI: 1.22-3.05) and discontinuers (wHR: 2.59, 95% CI: 0.94-7.12). Within this age band, the ADHD hazard was greater with SSRI/SNRI exposure for longer duration.

Associations with child ADHD symptoms

In the analysis at age 5 years, children of mothers who ever used SSRI/SNRI in pregnancy had a lower small risk of ADHD symptoms compared to non-medicated (weighted β (wβ): -0.23, 95% CI: -0.39, -0.08) or discontinuers (wβ: -0.18, 95% CI: -0.45, 0.09) (Table 2). The negative association between SSRI/SNRI exposure and ADHD symptoms in preschoolers seemed to be driven by duration of exposure, with larger effect size for exposure in 9-20 weeks. There was no difference in ADHD symptoms between groups according to longer exposure duration (Table 2).

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 3).

Further adjustment for pre-existing clinical depression/anxiety attenuated the observed associations in the age band 7-9 years (Table S7). Maternal pre-existing clinical depression/anxiety was independently associated with child ADHD in these analyses (weighted, adjusted HR: 1.34, 95% CI: (1.05-1.72)). Results of

other sensitivity analyses are given in the Supplement, Tables S8-10 and Figures S6-15, and these did not deviate from the main analysis.

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 underestimate of about 10% the observed point estimates, leading to an unaltered inference. When splitting the follow-up time, we observed that at pre- and early school-age children prenatally exposed to SSRI/SNRI have lower risk for ADHD diagnosis and symptoms than unexposed. 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 HR 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 psychiatric illness during and prior to during 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 and confounders, 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 via a validated instrument.[17] We carried out several sensitivity and sub-analyses to explore the robustness of our findings, as well as the role of confounding by maternal psychiatric indicators prior to gestation. In addition, we attempted to overcome the limitation of averaged HRs by estimating period-specific hazards; however, the built-in bias of differential selection on these results cannot be excluded. In addition, we cannot rule out the role of residual confounding by depression severity, genetic, environmental or familial factors, or even chance, on our findings.

Several limitations need mentioning. Symptoms of depressive and anxiety were not measured at baseline, but only at two time points in pregnancy. We relied on maternal self-report of depression/anxiety during or prior to pregnancy, which cannot replace a clinical diagnosis. Information on dosage is not available in MoBa. The ADHD symptom measure was mother-reported. 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. Also, the internal consistency of the CPRS-R was high. 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 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 ADHD-medications use, as well as parental self-report ADHD symptoms in a subsample.

Interpretation

In line with prior studies showing HR of magnitude 0.75-0.98[36,37] with 1.20 as upper bound of the pooled 95% CI,[38] we found no substantial difference in ADHD risk between prenatally SSRI/SNRI exposed children and children born to non-medicated women. Albeit with some uncertainty, the averaged hazard for ADHD with SSRI/SNRI exposure at any time during pregnancy was elevated (53% increased risk) when comparing to discontinuers, and likewise following 9-20 weeks exposure duration (2.1-fold increase). These contrasting

results across comparisons may be in part due to lower impulsive traits and thereby lower ADHD risk in discontinuers than in the other groups; however they do also suggest that antenatal depression/anxiety is possibly a key confounder. While confounding by indication was limited in the comparison with non-medicated, by restriction, discontinuers had no active psychiatric illness in pregnancy.[16] This risk of confounding did not emerge in the timing analysis, possibly because we fit methods able to account for time-varying depression symptom severity in pregnancy.[30]

Causal interpretation of HR is however risky, and effect estimates averaged over the duration of 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 in early childhood. Yet, an increased risk emerged in mid childhood (7-9 years). This temporal trend was apparent across all the window of exposures, except for SSRI/SNRI in late pregnancy, which partly aligns with the result of Boukhris *et al* .[40] Further comparison with prior research is difficult since adjusted survival curves are often not presented, the follow-up time is too short, or it is unclear whether the HRs were constant over time.[36,39,41-43]

The observed ADHD risk reduction at 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 prior studies that controlled for maternal mood disorders, genetic liability or familial environment.[44] Alternative explanations are however possible: 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 an association between SSRI/SNRI ever exposure (93% increased hazard) or for 9-20 weeks duration (2.8-fold increased hazard), relative to non-medicated 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 frailty, small sample size, or competing risks cannot be ruled out. If the former explanation holds true, 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 the environmental exposure to depression or SSRI/SNRI on ADHD across ages, remains untestable in the current study.[49]

Our results document the confounding role of maternal pre-existing clinical depression/anxiety, yielding a risk attenuation of 18-20% in the weighted effect estimates. This factor was independently associated with child ADHD (34% increased risk), which replicates prior research.[40] It is reasonable that maternal psychiatric status prior to pregnancy confound the antidepressant-ADHD association via unfavorable health behaviors, poor nutrition, or genetic make-up.

CONCLUSIONS

When the ADHD hazard was averaged over the duration of the study's follow-up, there was no association between prenatal SSRI/SNRI exposure and ADHD in offspring, and exposure misclassification could 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 psychiatric indicators in this study, does not support a causal link between SSRI/SNRI and child ADHD. Future research is needed on the age-specific associations between antidepressants in pregnancy and ADHD subtypes trajectories.

Acknowledgments: The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this on-going cohort study.

Funding : This project is funded through the HN's ERC Starting Grant "DrugsInPregnancy" (grant no. 678033). EY is supported by the Norwegian Research Council (grant no. 262177 and 288083). AL is supported by the Norwegian Research Council (grant no. 288696). The funders had no role in the analyses, interpretation of results, or the writing of this manuscript.

Disclosure of interest: no conflicts to declare.

Contributions of authors: 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 26th March 2015 (reference number: 2015/442/REK Sør-Øst).

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).

References

1. Huybrechts KF, Palmsten K, Mogun H, et al. National trends in antidepressant medication treatment among publicly insured pregnant women. *Gen Hosp Psychiatry.* 2013;35(3):265-271.

2. Zoega H, Kieler H, Norgaard M, et al. Use of SSRI and SNRI Antidepressants during Pregnancy: A Population-Based Study from Denmark, Iceland, Norway and Sweden. *PLoS One.* 2015;10(12):e0144474.

3. Charlton RA, Jordan S, Pierini A, et al. Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. *BJOG.*2015;122(7):1010-1020.

4. Gaspar P, Cases O, Maroteaux L. The developmental role of serotonin: news from mouse molecular genetics. *Nat Rev Neurosci.*2003;4(12):1002-1012.

5. Sujan AC, Oberg AS, Quinn PD, D'Onofrio BM. Annual Research Review: Maternal antidepressant use during pregnancy and offspring neurodevelopmental problems - a critical review and recommendations for future research. *J Child Psychol Psychiatry.* 2019;60(4):356-376.

6. Man KKC, Chan EW, Ip P, et al. Prenatal antidepressant exposure and the risk of attention-deficit hyperactivity disorder in children: A systematic review and meta-analysis. *Neurosci Biobehav Rev.*2018;86:1-11.

7. Hjorth S, Bromley R, Ystrom E, Lupattelli A, Spigset O, Nordeng H. Use and validity of child neurodevelopment outcome measures in studies on prenatal exposure to psychotropic and analgesic medications - A systematic review. *PLoS One.* 2019;14(7):e0219778.

8. Lupattelli A, Wood M, Ystrom E, Skurtveit S, Handal M, Nordeng H. Effect of Time-Dependent Selective Serotonin Reuptake Inhibitor Antidepressants During Pregnancy on Behavioral, Emotional, and Social Development in Preschool-Aged Children. *J Am Acad Child Adolesc Psychiatry.* 2018;57(3):200-208.

9. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision.*Lancet Psychiatry.* 2018;5(2):175-186.

10. Magnus P, Birke C, Vejrup K, et al. Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol.*2016;45(2):382-388.

11. Magnus P, Irgens LM, Haug K, et al. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol.*2006;35(5):1146-1150.

12. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand.* 2000;79(6):435-439.

13. Norwegian Institute of Public Health. Norwegian Prescription Database (NorPD). https://www.fhi.no/en/hn/health-registries/norpd/. Published 2019. Accessed 19 March, 2019.

14. Bakken IJ, Suren P, Haberg SE, Cappelen I, Stoltenberg C. [The Norwegian patient register–an important source for research].*Tidsskr Nor Laegeforen.* 2014;134(1):12-13.

15. Hernan MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology.*2008;19(6):766-779.

16. Wood ME, Lapane KL, van Gelder M, Rai D, Nordeng HME. Making fair comparisons in pregnancy medication safety studies: An overview of advanced methods for confounding control. *Pharmacoepidemiol Drug Saf.* 2018;27(2):140-147.

17. Strand BH, Dalgard OS, Tambs K, Rognerud M. 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). *Nord J Psychiatry.* 2003;57(2):113-118.

18. Tambs K, Moum T. How well can a few questionnaire items indicate anxiety and depression? *Acta Psychiatr Scand.* 1993;87(5):364-367.

19. Norwegian Institute of Public Health. The Nowegian Mother and Child Cohort Study. Questionnaires. Norwegian Institute of Public Health. https://fhi.no/en/studies/moba/for-forskere-artikler/questionnaires-from-moba/. Accessed August 5, 2019.

20. WHO Collaborating Centre for Drugs Statistics Methodology. ATC/DDD index 2012. http://www.whocc.no/atc_ddd_index/. Accessed 17 March, 2017.

21. Skurtveit S, Selmer R, Tverdal A, Furu K, Nystad W, Handal M. Drug exposure: inclusion of dispensed drugs before pregnancy may lead to underestimation of risk associations. *J Clin Epidemiol.*2013;66(9):964-972.

22. Lupattelli A, Chambers CD, Bandoli G, Handal M, Skurtveit S, Nordeng H. Association of Maternal Use of Benzodiazepines and Z-Hypnotics During Pregnancy With Motor and Communication Skills and Attention-Deficit/Hyperactivity Disorder Symptoms in Preschoolers.*JAMA Netw Open.* 2019;2(4):e191435.

23. Ørstavik R, Gustavson K, Rohrer-Baumgartner N, et al. *ADHD i Norge.* Folkehelseinstituttet 2016.

24. ADHD and hyperkinetic disorder. In: *Rutter's Child and Adolescent Psychiatry.* 738-756.

25. Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol.*1998;26(4):257-268.

26. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology.* 2011;22(5):745.

27. Bateman BT, Mhyre JM, Hernandez-Diaz S, et al. Development of a comorbidity index for use in obstetric patients. *Obstet Gynecol.*2013;122(5):957-965.

28. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. The lifetime history of major depression in women. Reliability of diagnosis and heritability. *Arch Gen Psychiatry.* 1993;50(11):863-870.

29. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies.*Stat Med.* 2015;34(28):3661-3679.

30. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology.*2000;11(5):550-560.

31. Rubin DB. *Multiple imputation for nonresponse in surveys.* New York: Wiley; 1987.

32. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* 2009;338:b2393.

33. Moodie EE, Delaney JA, Lefebvre G, Platt RW. Missing confounding data in marginal structural models: a comparison of inverse probability weighting and multiple imputation. *The international journal of biostatistics.* 2008;4(1):Article 13.

34. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol.* 2009;23(6):597-608.

35. Biele G, Gustavson K, Czajkowski NO, et al. Bias from self selection and loss to follow-up in prospective cohort studies. *Eur J Epidemiol.* 2019;34(10):927-938.

36. Malm H, Brown AS, Gissler M, et al. Gestational Exposure to Selective Serotonin Reuptake Inhibitors and Offspring Psychiatric Disorders: A National Register-Based Study. *J Am Acad Child Adolesc Psychiatry.* 2016;55(5):359-366.

37. Grzeskowiak LE, Morrison JL, Henriksen TB, et al. Prenatal antidepressant exposure and child behavioural outcomes at 7 years of age: a study within the Danish National Birth Cohort. *BJOG.*2016;123(12):1919-1928.

38. Jiang HY, Peng CT, Zhang X, Ruan B. Antidepressant use during pregnancy and the risk of attention-deficit/hyperactivity disorder in the children: a meta-analysis of cohort studies. *BJOG.*2018;125(9):1077-1084.

39. Hernán MA. The Hazards of Hazard Ratios. *Epidemiology.*2010;21(1):13-15.

40. Boukhris T, Sheehy O, Berard A. Antidepressant Use in Pregnancy and the Risk of Attention Deficit with or without Hyperactivity Disorder in Children. *Paediatr Perinat Epidemiol.* 2017.

41. Man KKC, Chan EW, Ip P, et al. Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study. *BMJ.* 2017;357:j2350.

42. Sujan AC, Rickert ME, Oberg AS, et al. Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring. *JAMA.*2017;317(15):1553-1562.

43. Laugesen K, Olsen MS, Telen Andersen AB, Froslev T, Sorensen HT. In utero exposure to antidepressant drugs and risk of attention deficit hyperactivity disorder: a nationwide Danish cohort study. *BMJ open.* 2013;3(9):e003507.

44. El Marroun H, White T, Verhulst FC, Tiemeier H. Maternal use of antidepressant or anxiolytic medication during pregnancy and childhood neurodevelopmental outcomes: a systematic review. *Eur Child Adolesc Psychiatry.* 2014;23(10):973-992.

45. Maoz H, Goldstein T, Goldstein BI, et al. The effects of parental mood on reports of their children's psychopathology. *J Am Acad Child Adolesc Psychiatry.* 2014;53(10):1111-1122.e1115.

46. Galéra C, Côté SM, Bouvard MP, et al. Early Risk Factors for Hyperactivity-Impulsivity and Inattention Trajectories From Age 17 Months to 8 Years. *Arch Gen Psychiatry.* 2011;68(12):1267-1275.

47. Schrantee A, Lucassen PJ, Booij J, Reneman L. Serotonin transporter occupancy by the SSRI citalopram predicts default-mode network connectivity. *Eur Neuropsychopharmacol.* 2018;28(10):1173-1179.

48. Samuele Cortese, M.D., Ph.D. ,, Clare Kelly, Ph.D. ,, Camille Chabernaud, Ph.D. ,, et al. Toward Systems Neuroscience of ADHD: A Meta-Analysis of 55 fMRI Studies. *Am J Psychiatry.*2012;169(10):1038-1055.

49. Eilertsen EM, Gjerde LC, Kendler KS, et al. Development of ADHD symptoms in preschool children: Genetic and environmental contributions. 2019;31(4):1299-1305.

Figure Legends

Figure 1: Period-specific associations of SSRI/SNRI windows of exposure with child ADHD

Point estimates < 1: Favors SSRI/SNRI exposure. Point estimates > 1 favors 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.

Abbreviations: SSRI=selective serotonin reuptake inhibitors; SNRI= Serotonin-norepinephrine reuptake inhibitors.

In the age band [?] 9 years no period-specific HR could be computed for the > 20 weeks and timing windows in Panel A and in all exposure windows in Panel B because of few ADHD cases.

Hosted file

`Tables.pdf` available at https://authorea.com/users/361902/articles/483173-attention-deficit-hyperactivity-disorder-in-children-following-prenatal-exposure-to-antidepressants-results-from-the-norwegian-mother-father-and-child-cohort-study