MATERNAL USE OF PSYCHIATRIC MEDICATIONS DURING PREGNANCY AND ADVERSE BIRTH OUTCOMES AND NEURODEVELOPMENTAL PROBLEMS IN OFFSPRING

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Understanding consequences of prenatal exposure to psychiatric and analgesic medications is important because use of these medications among pregnant women is relatively common and increasing. Rodent experiments have shown effects of perinatal exposure to specific medications; however, these findings might not apply to humans. Human observational studies have been used to study prenatal exposure to psychiatric and analgesic medications rather than randomized control trials due to ethical concerns about exposing offspring to potentially harmful substances. However, it is unclear the extent to which the statistical associations documented in observational studies are due to causal mechanisms or background factors that differ among exposed and unexposed pregnancies (i.e., confounding factors).

Therefore, the aim of my dissertation research was to evaluate consequences of prenatal exposure to psychiatric and analgesic medications on risk for adverse birth outcomes and neurodevelopmental problems by seeking converging evidence from multiple observational designs that target both *measured* and *unmeasured* confounding. The first study showed that after accounting for confounding, prenatal antidepressant exposure was associated with a small increased risk of preterm birth (PTB) but no increased risk of small for gestational age (SGA), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD). The second study suggested that observed associations between prenatal exposure to prescribed opioid analgesics (POAs) and risk for PTB and SGA were largely due to unmeasured confounding factors, although I could not rule out small independent associations. The third

study evaluated the consequences of combined exposure to POAs and selective-serotine reuptake inhibitor antidepressants on risk for PTB and SGA and suggested that the medications do not interact to increase the risk of either outcome.

These findings may provide reassurance to women considering antidepressant and POA use during pregnancy. They also highlight the importance of screening pregnant women and women of childbearing age and providing evidence-based treatments to at-risk women.

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I. Introduction

The introduction is based on a published review paper:

Sujan, A.C., Oberg, A.S., Quinn, P.D, & D'Onofrio, B.M. (2019*).* Annual research review: Maternal antidepressant use during pregnancy and offspring neurodevelopmental problems – a critical review and recommendations for future research. *Journal of Child Psychology and Psychiatry, 60*(4):356-376. doi: 10.1111/jcpp.13004. PMCID: PMC6438736.

Background

The developmental origins of health and disease (DOHaD) hypothesis is a framework that originated from research linking fetal development, particularly birth weight, to adult health, particularly cardiovascular health. The hypothesis was based on the premise that insults during sensitive periods *causally* impact development and became a popular framework for stipulating causal effects of early risk factors on development across the lifespan.[1]

The DOHaD framework can be applied to study possible teratogens – agents that alter fetal development and, thereby, increase the risk of adverse perinatal outcomes (e.g., death, reduced fetal growth, and birth defects) or neurological impairments that appear later in childhood.[2,3] Perhaps the most salient example of a teratogen is thalidomide – a medication that was widely prescribed to treat nausea during pregnancy until it was found to cause severe birth defects.[2] Though the teratogenic effects of thalidomide are well established, the potential effects of many other medications, including antidepressants and prescribed opioid analgesics (POAs), are far less clear.[4-6]

Understanding the consequences of prenatal exposure to antidepressant and opioid analgesics is important because use of these medications during pregnancy is common and increasing. For example, in a sample of 1.9 million insured pregnant women in the U.S., approximately 2% filled a prescription for a selective serotonin reuptake inhibitor (SSRI) antidepressant in 2001, whereas 12% filled a prescription for a SSRI in 2013.[7] Similarly, in a sample of 1.1 million U.S. pregnant women, approximately 19% received a POA in 2000, whereas 23% received a POA in 2007.[8] Concerns that prenatal exposure to these medications may be harmful to fetal development have led some medical professionals to recommend that pregnant women avoid using them during pregnancy.[e.g.,9]

Rodent studies have shown that perinatal exposure to antidepressant and opioid medications causes abnormalities in brain structure and function and behavior.[10-19] Additionally, observational studies with humans have shown that these medications cross the placenta[20-23] and can be found in amniotic fluid[24-26] and cord blood.[26-31] Observational studies with humans have also documented that prenatal exposure to antidepressants and POAs are associated with adverse birth outcomes (e.g., preterm birth [PTB], reduced fetal growth, and birth defects)[6,32-34] and neurodevelopmental problems (e.g., autism spectrum disorder [ASD] and attention-deficit/hyperactivity disorder [ADHD]).[35]

However, it is important to consider that these findings may not reflect a causal effect of prenatal exposure to the medications. While randomization in rodent experiments helps ensure that there are no systematic differences between those exposed and unexposed, it is unclear if effects in rodents apply to humans given between-species differences related to pregnancy and drug metabolism rates.[36] Additionally, associations documented in observational studies with humans may be due to systematic differences between exposed and unexposed offspring. Unlike randomized control trials where the exposed and unexposed group could theoretically be swapped without altering the results, exposed and unexposed individuals in observational studies are not exchangeable. Therefore, in addition to a potential causal influence of prenatal exposure, other factors that differ between exposed and unexposed offspring could contribute to observed associations. Factors other than the exposure of interest that contribute to an observed association are referred to as confounding factors. It is important to note that multiple plausible influences, including causal mechanisms and/or confounding factors, could simultaneously contribute to observed associations between maternal use of medications during pregnancy and offspring outcomes.

Potential processes influencing associations with prenatal psychiatric medication exposure

I will use maternal antidepressant use during pregnancy and offspring neurodevelopmental problems to illustrate how multiple factors could contribute to an observed association between maternal use of a medication during pregnancy and an adverse offspring outcome. Figure I.1 presents a simplified model to illustrate some of the main processes through which prenatal antidepressant exposure could be associated with neurodevelopmental problems.

As depicted by the solid arrows labeled *a* and *b* in Figure I.1, prenatal antidepressant exposure could cause an increased risk of neurodevelopmental problems through mechanisms of action. For example, the developmental hyperserotonemia (DHS) model of autism postulates that high levels of maternal blood serotonin could enter the developing brain of the fetus and cause a loss of serotonin receptors through a negative feedback mechanism. In support of the DHS model, research has documented that individuals with ASD have elevated blood levels of serotonin[37,38] and decreased activity, synthesis, and binding potential of serotonin in several brain areas.[39-43]

Another possible causal pathway is through adverse birth outcomes, such as reduced fetal growth and shorter gestational periods. Numerous studies, including studies that used advanced methods to account for potential confounding factors, have found associations between prenatal antidepressant exposure and adverse birth outcome[e,g,32,44,45] and associations between adverse birth outcomes and neurodevelopmental problems, including ASD and ADHD.[e.g.,46-49]

Aside from causal mechanisms, however, there are several non-causal influences that could partially or fully explain observed associations between prenatal antidepressant exposure and neurodevelopmental problems. In order to introduce this possibility, I review several such processes below.

As illustrated in Figure I.1 by the dotted arrow *c*, maternal indications for antidepressant use influence risk of prenatal antidepressant exposure. Although antidepressants can be prescribed to treat a variety of conditions – such as insomnia, pain, and migraines – antidepressants are primary used to treat depressive and anxiety disorders,[50] which can be influenced by stressful life events.[e.g., 51,52] Moreover, several observational studies have shown that stress during pregnancy, as well as depression, anxiety, and other maternal psychiatric conditions are associated with increased risk of offspring ASD[53,54] and ADHD.[54-59] That is, as shown by dotted arrow labeled *d* in Figure I.1, maternal conditions could influence offspring neurodevelopment. For example, maternal depressive symptoms may lead to poorer parenting practices,[e.g., 60] which in turn are associated with offspring neurodevelopmental problems.[e.g., 61] Alternatively, as shown by the dotted arrow labeled *e* in Figure I.1, maternal conditions like depression, could also influence mechanisms, such as adverse birth outcomes.[62] Thus, there are multiple plausible pathways through which that the maternal condition for which antidepressants are used during pregnancy could contribute to a higher likelihood for the exposed offspring to develop ASD or ADHD.

As shown by the dotted arrows labeled *f* in Figure I.1, other environmental factors that could influence indications for maternal antidepressant use may, through some mechanism of action, also influence the risk of neurodevelopmental problems. There are several plausible candidates for such environmental common causes of prenatal antidepressant exposure and neurodevelopmental outcomes. For example, low socioeconomic status predicts the development of depression[63] and is associated with reduced availability of healthy foods,[64] and poorer nutrition has been linked with cognitive,[65] behavioral,[66] and attention[67] problems. Maternal conditions that could contribute to an adverse intrauterine environment, such as preexisting

health problems (e.g., high body mass index, diabetes, and chronic hypertension), are also associated with antidepressant use during pregnancy, and, thus, may confound associations.

Additionally, prenatal antidepressant exposure and neurodevelopmental problems may share genetic influences. The phenomenon that the same genetic factors can influence multiple phenotypes and, therefore, confound associations between phenotypes is known as biological pleiotropy.[68] The potential influence of biological pleiotropy is depicted by the dotted arrows labeled *g* on Figure I.1, which show that genetic factors could influence indications for maternal antidepressant use during pregnancy, as well as the liability for neurodevelopmental problems in offspring. Research has provided support for the influence of biological pleiotropy. Specifically, twin studies[69,70] and genome-wide association studies[71] have suggested that genetic liability is shared across internalizing problems – such as depression and anxiety disorders – and neurodevelopmental disorders – such as ASD and ADHD.

In sum, this example of maternal antidepressant use during pregnancy and offspring neurodevelopmental problems illustrates that observed associations between prenatal exposure to medications and adverse offspring outcomes could be due to several processes, including a causal effect of the exposure, indications for maternal use of the medication, environmental common causes, and/or biological pleiotropy. Importantly, these influences are not necessarily mutually exclusive – an association could be partly due to a causal effect of exposure to the medication and partly due to pre-existing background factors, indicating that the true increase in risk attributable to prenatal exposure to the medication is nonzero but less than might be expected based on the overall association.

Observation methods to study the consequences of maternal medication use during pregnancy

Pregnant women are typically excluded from randomized clinical trials testing the safety of medication use due to ethical concerns about exposing developing fetuses to potentially harmful substances.[72] Therefore, researchers have to rely on observational data and methodological approaches to try to account, in varying degrees, for the influence of background factors that could contribute to the associations with prenatal exposure to medications.

Several different types of observational designs can be used to study medication use during pregnancy and offspring outcomes. Some of these designs are better able to test the role of potential confounding factors than others. However, all methods have specific limitations and require assumptions when interpreting the results. I briefly review the strengths and limitations of these designs below.

Designs that target measured potential confounders

The majority of observational studies have used methods to account for characteristics that have been measured by the researchers. In particular, most studies have relied on using measured characteristics as statistical covariates in regression models. This method models the relationships between the measured characteristic and the outcome. The method does not model the relationship between the measured characteristics and the exposure status. Therefore, it is possible that the covariate distribution is very different between exposed and unexposed offspring. In fact, it is possible that there are no exposed and unexposed offspring included in analyses that are similar across all measured characteristics.[73]

Rather than including measured characteristics as covariates in regression models, researchers can utilize methods that use measured characteristics to model relationships between the characteristics and the *exposure*. One method that has been commonly used, particularly for studies on antidepressant use during pregnancy,[e.g.,74-80] is restricting the comparison group to

offspring of women with the underlying condition (e.g., major depressive disorder) who did not use the medication during pregnancy. This method creates exposed and unexposed groups of offspring that both have mothers with the conditions and, thereby, helps account for confounding by indication. However, this method does not account for differences in severity of indication between medicated and unmediated mothers and only matches the exposed and unexposed groups on one measured characteristic (psychiatric conditions).

Unlike restricting comparison groups to mothers with the underlying conditions, propensity score methods can model the relationship between *multiple* measured characteristics and the exposure. A propensity score is a conditional probability of an exposure status given an observed set of covariates. Propensity scores can be used to match exposed and unexposed offspring with similar scores. This method, known as propensity score matching, may result in some offspring without matches being excluded from the dataset. However, the resulting dataset will be balanced on covariates among exposed and unexposed offspring, a property that would be expected if randomization had occurred because balanced covariates cannot be associated with the exposure and, therefore, cannot be confounders.

Another method that uses propensity scores is inverse probability treatment weighting (IPTW). This method would use measured characteristics to create a weight for each offspring in the dataset that represents the probability of having the offspring's given exposure status given his/her observed characteristics. Including these weights in the analyses makes offspring that were less likely to have their exposure status given their observed characteristics contribute to analyses more. Like propensity scores matching, IPTW results in a study population in which covariates and exposure status are unassociated. More information on propensity score methods is available elsewhere.[73]

It is important to note that any method, including propensity score methods, that only adjusts for measured characteristics is unlikely to adequately account for confounding because researchers realistically cannot measure every salient plausible confounding factor.[81] Furthermore, error in the measurement of the characteristics may lead researchers to adjust for far less confounding than intended.[82]

Designs that target unmeasured potential confounding

To more rigorously assess the consequences of prenatal exposure to medications, some researchers have used measured covariates in combination with advanced observational methods with design features that either account for or evaluate the potential role of *unmeasured* confounding factors. Although such designs are typically able to capture more background factors than possible with measured characteristics alone, the net ability to capture confounding factors will depend on the degree to which these are among the targeted unmeasured factors and measured characteristics combined. I briefly review several methods that target unmeasured confounding below.

Paternal medication use as a negative control. The negative control design compares what happens to the association with an offspring outcome if the exposure to maternal use of the medication during pregnancy is replaced with exposure to paternal use of the medication during the pregnancy period. By definition, an ideal negative control is influenced by all of the same confounding factors as the exposure of interest but has no causal effect on the outcome. Given that paternal medications use during the pregnancy period is unlikely to result in fetal exposure, any observed association between paternal use and an offspring outcome suggests that the observed association with maternal use is influenced by confounding to some extent. Given that confounding factors and a causal influence of exposure to the medication could simultaneously

contribute to an association, a paternal association would have to be similar in magnitude to the maternal association in order to completely rule out a causal effect of intrauterine exposure to the medication. In other words, the paternal use association helps indicate the degree of confounding in the maternal use association.

Importantly, the negative control design rests on the assumption that maternal and paternal medication use are influenced by the same confounding factors. However, this assumption could be violated for several reasons. For example, father and mothers with the same indication may vary in their likelihood of being prescribed and using the medication. It is possible that maternal use of the medication during pregnancy is associated with more severe symptoms than paternal use because mothers may be more inclined to discontinue medication use during pregnancy due to concerns about fetal exposure. Another limitation of this design is that it assumes equal measurement error of medication use across mothers and fathers. More information about negative control analyses is available elsewhere.[83-85]

Comparative safety design. The comparative safety design compares individuals exposed to a medication under study to individuals exposed to an alternative medication used to treat the same condition as the medication under study. A null association with exposure to the medication under study compared to exposure to the alternative medication would suggest that the medication under study is not more harmful than the alternative medication. The comparative safety design accounts for all unmeasured confounding factors that are common to the use of both types of medications, such as common indications. However, an observed null association is not necessarily indicative of a lack of effect of exposure to the medication under study because it is possible that both medications influence the offspring outcome through different etiological

mechanisms. More information about the use of alternative medications as comparators is available elsewhere.[86,87]

Timing of exposure comparison. The timing of exposure design compares the offspring outcome following maternal use of the medication *before but not during pregnancy*, to the offspring outcome following maternal use of the medication *during pregnancy*. This design accounts for confounding factors shared by women treated with the medication around the time of pregnancy, such as having a condition for which treatment is indicated. The finding that risk of the outcome is similar across the exposure time-periods would be inconsistent with a causal effect because use before pregnancy is unlikely to result in fetal exposure.

There are two key limitations of the design. First, it assumes that preconception medication exposure does not affect offspring development. Second, the design also does not account for unmeasured confounding factors that differ between the mothers who use the medication during pregnancy and those who only use the medication before pregnancy. More information about timing of exposure comparison designs is available elsewhere.[85]

Sibling comparison. Siblings share 50% of their segregating genes on average and often have similar early environments. The sibling-comparison design makes use of these similarities. A contrast of siblings that are discordant for prenatal medication exposure will account for all unmeasured genetic and environmental factors that make siblings similar, including all maternal characteristics and other factors that remain stable across pregnancies. Similar risk of an adverse outcome among differentially exposed siblings would suggest that genetic and/or environmental factors shared by siblings rather than a causal effect of prenatal exposure to the medication increases the risk of the outcome. Given that genetic confounding is likely to exist,[68] this design

is particularly helpful in drawing causal inferences because it helps test for genetic and family-level confounding.

Although sibling comparisons provide a rigorous test of confounding by familial factors, the design by itself cannot account for unmeasured confounding by factors that vary across a woman's pregnancies. However, in order to account for confounding by factors that vary across pregnancies, researchers can use measured timing-varying characteristics as statistical covariates in combination with sibling-comparison designs. Sibling-comparison designs also assume no carry-over effects from the exposed siblings to the unexposed siblings (e.g., medication use during one pregnancy affecting subsequent pregnancies). Additionally, it is possible that an observed attenuation in associations in sibling-comparison studies may be due to random measurement error or mediators shared by the siblings. Sibling comparisons also require large samples to obtain an adequate number of discordant siblings. More information about sibling comparison designs is available elsewhere.[88-92]

Summary and conclusion regarding observation methods to study the consequences of maternal medication use during pregnancy

There are several observational designs that researchers can use to make causal inferences about prenatal exposure to medications. Given that all methods have their own set of strengths and limitations and it is not feasible for researchers to measure every salient plausible confounding factor, especially without measurement error, researchers should focus on seeking converging evidence from methods that are able to account for both measured and unmeasured potential confounding factors.

Dissertation research

Given that observed associations with prenatal exposure to antidepressants and POAs could be due to causal mechanisms or confounding factors, uncertainty remains regarding the short- and long-term effects of maternal use of these medication during pregnancy. Therefore, my dissertation research aimed to evaluate the consequences of exposure to antidepressants and POAs during pregnancy on adverse birth outcomes and neurodevelopmental problems in offspring by seeking converging evidence from multiple observational methods that target both unmeasured and measured confounding factors.

My dissertation research comprised three papers. The first paper evaluated the consequences of prenatal antidepressant exposure on risk of adverse birth outcomes and neurodevelopmental problems.[44] The second paper evaluated the consequences of prenatal POA exposure on risk for adverse birth outcomes.[93] The third paper evaluated combined use of POAs and SSRI antidepressants during pregnancy on risk of adverse birth outcomes.[94] The birth outcomes I studied were PTB (birth before 37 gestational weeks) and small for gestational age (SGA; birth weight more than 2 standard deviations below the expected weight for gestational age); and the neurodevelopmental problems I studied were ASD and ADHD.

Dataset

For all the projects, I conducted analyses on a dataset based on linking numerous Swedish population registers via a unique civic registration number assigned to all citizens at birth and to immigrants upon arrival to the country. The government allows linkages for research,[95] which has led to extensive psychiatric epidemiology studies.[96, 97] I briefly describe several registers in Table I.1 and present more detailed information about four key registers below in the text.

First, the Medical Birth Register (MBR)[98-100] contains data on all live births since 1973. The register consistently covers more than 98% of all births (≈105,000 yearly). Information from medical charts has been recorded in the register through computerized systems since 1982 and includes (a) antenatal visits, (b) the delivery, (c) the pediatric exam of the newborn, and (d) the epicrisis upon discharge. The validity of key variables is high.[98-100] Beginning in 1996, The MBR includes information on maternal-reported medication use at the first antenatal visit. This visit typically occurs between the 10th and 12th week of pregnancy. Therefore, information on medication use obtained from the MBR is presumed to represent first-trimester use.

Second, the Multi-Generation Register (MGR)[101] links all Swedish residents to their parents, adoptive or biological, thereby allowing for the identification of all family structures.

Third, the National Patient Register (NPR)[102] provides data on all psychiatric inpatient visits since 1973 and specialized outpatient care since 2001. Every record has a date and the primary and secondary diagnoses assigned by the treating medical doctor according to the International Classification of Diseases (ICD) criteria.[103] The use of registers in psychiatric research is well established,[97] and the general validity of the Swedish NPR is high.[104]

Fourth, the Prescribed Drug Register (PDR)[105,106] provides data on the dispensing of all prescribed pharmaceuticals in the entire population since July 2005.[107] Doses and amounts prescribed, along with dates of prescription and dispensing, allow for timing and degree of exposure. Furthermore, the register includes information about the clinic and the specialty of the prescribing physician for each filled prescription.

The stability, reliability, and coverage of Swedish population registers render them uniquely suited for epidemiological studies (e.g., prospective data collection and minimal loss to follow-up) and invaluable to designs requiring information on family relations. The Swedish

setting also offers unique advantages when studying risks of psychiatric medications. Sweden's universal healthcare system removes important barriers to treatment access, which could contribute to confounding in the studies of psychiatric medications and offspring outcomes conducted in other countries. Furthermore, Swedish medical practice has historically been more conservative in their use of psychiatric medications than the United States,[108] which provides an opportunity to examine psychiatric medications and their consequences in an environment less contaminated by diversion, misuse, and inappropriate prescribing (e.g., so-called pill mills).

Table I.1. Swedish Registers

Register	Key Information
Medical Birth Registry (MBR)	Detailed information on more than 98% of pregnancies in the country since 1973.[98-100]
Multi-Generation Register (MGR)	Information about all biological and adoptive relationships (e.g. parents, siblings).[109]
National Patient Register (NPR)	Information, including discharge diagnosis, for all psychiatric inpatient visits since 1973 and outpatient care since 2001.[103]
Prescribed Drug Register (PDR)	Data on all prescribed and filled pharmaceuticals since July 2005.[106]
Education Register	Contains highest level of education for each adult per year and grades and achievement tests for all students at grade 9.[110]
Cause of Death Register (CDR)	Data on principal and contributing causes of death since 1958.
Integrated Database for Labour Market Research (LISA)	Annual socio-economic data (e.g., income, education, employment) for each individual since 1990.[111]
Statistics Sweden Regional Register (SSRS)	Annual place of residence information for each individual, including Small Area Market Statistics (SAMS), which are small geographic units.[112]
National Crime Register (NCR)	All criminal convictions since 1973 of those 15+ yrs. old [113,114]
Migration Register	Information on all emigrations and immigrations.
Conscript Register	Assessments of males at 18 yrs. since 1970.[115]
Swedish Twin Register (STR)	In-depth assessments of psychopathology from the world's largest twin register.[116]

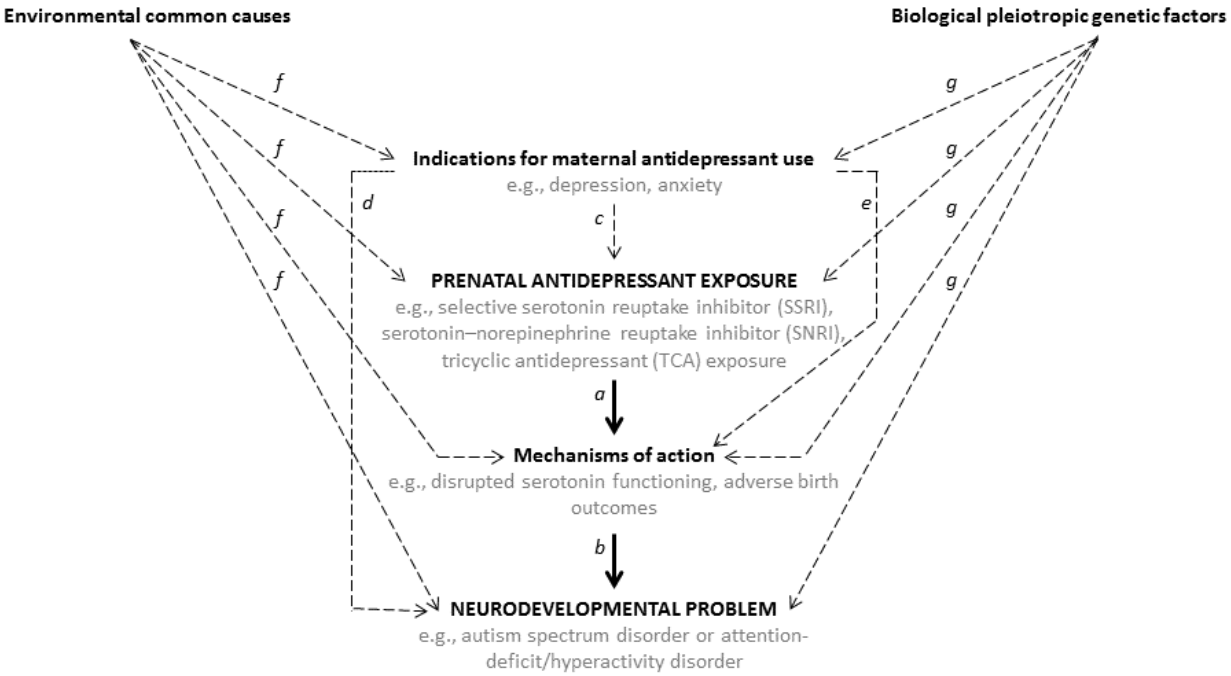

Figure I.1. Hypothesized influences on neurodevelopmental outcomes among offspring exposed to antidepressants during pregnancy. Solid lines *a* and *b* represent a plausible causal pathway from prenatal antidepressant exposure to neurodevelopmental problems through proximal mechanisms of action. Dashed lines represent plausible confounding from indications for maternal antidepressant use (path *c*, *d*, and *e*), environmental common causes (paths *f*), and/or biological pleiotropic genetic factors (path *g*).

References

1. Barker DJP. *Mothers, babies and health in later life.* 2nd ed. Edinburgh: Churchill Livingstone; 1998.
2. Alwan S, Chambers CD. Identifying Human Teratogens: An Update. *Journal of Pediatric Genetics.* 2015;4(2):39-41.
3. Georgieff MK, Tran PV, Carlson ES. Atypical fetal development: Fetal alcohol syndrome, nutritional deprivation, teratogens, and risk for neurodevelopmental disorders and psychopathology. *Development and Psychopathology.* 2018;30(3):1063-1086.
4. Galbally M, Crabb C, Snellen M. Designing research that can untangle the effects in pregnancy of pharmacological treatments for mental disorders. *The Lancet Psychiatry.* 2018;5(8):608-610.
5. Rubin R. Addressing barriers to inclusion of pregnant women in clinical trials. *JAMA.* 2018.
6. Lind JN, Interrante JD, Ailes EC, et al. Maternal Use of Opioids During Pregnancy and Congenital Malformations: A Systematic Review. *Pediatrics.* 2017;139(6).
7. Andrade SE, Reichman ME, Mott K, et al. Use of selective serotonin reuptake inhibitors (SSRIs) in women delivering liveborn infants and other women of child-bearing age within the US Food and Drug Administration's Mini-Sentinel program. *Archives of Womens Mental Health.* 2016;19(6):969-977.
8. Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. *Obstet Gynecol.* 2014;123(5):997-1002.

9. Campagne DM. Fact: antidepressants and anxiolytics are not safe during pregnancy. *European journal of obstetrics, gynecology, and reproductive biology.* 2007;135(2):145-148.

10. Lee LJ. Neonatal fluoxetine exposure affects the neuronal structure in the somatosensory cortex and somatosensory-related behaviors in adolescent rats. *Neurotox Res.* 2009;15(3):212-223.

11. Simpson KL, Weaver KJ, de Villers-Sidani E, et al. Perinatal antidepressant exposure alters cortical network function in rodents. *Proceedings of the National Academy of Sciences of the United States of America.* 2011;108(45):18465-18470.

12. Weaver KJ, Paul IA, Lin RC, Simpson KL. Neonatal exposure to citalopram selectively alters the expression of the serotonin transporter in the hippocampus: dose-dependent effects. *Anat Rec (Hoboken).* 2010;293(11):1920-1932.

13. Rodriguez-Porcel F, Green D, Khatri N, et al. Neonatal exposure of rats to antidepressants affects behavioral reactions to novelty and social interactions in a manner analogous to autistic spectrum disorders. *Anat Rec (Hoboken).* 2011;294(10):1726-1735.

14. Zimmerberg B, Germeyan SC. Effects of neonatal fluoxetine exposure on behavior across development in rats selectively bred for an infantile affective trait. *Dev Psychobiol.* 2015;57(2):141-152.

15. Ko MC, Lee LJ, Li Y. Long-term consequences of neonatal fluoxetine exposure in adult rats. *Dev Neurobiol.* 2014;74(10):1038-1051.

16. Schaefer TL, Grace CE, Braun AA, et al. Cognitive impairments from developmental exposure to serotonergic drugs: citalopram and MDMA. *Int J Neuropsychopharmacol.* 2013;16(6):1383-1394.

17. Sprowles JL, Hufgard JR, Gutierrez A, et al. Perinatal exposure to the selective serotonin reuptake inhibitor citalopram alters spatial learning and memory, anxiety, depression, and startle in Sprague-Dawley rats. *Int J Dev Neurosci.* 2016;54:39-52.

18. Byrnes EM, Vassoler FM. Modeling prenatal opioid exposure in animals: Current findings and future directions. *Front Neuroendocrinol.* 2017.

19. Farid WO, Dunlop SA, Tait RJ, Hulse GK. The effects of maternally administered methadone, buprenorphine and naltrexone on offspring: Review of human and animal data. *Current Neuropharmacology.* 2008;6(2):125-150.

20. Loebstein R, Lalkin A, Koren G. Pharmacokinetic changes during pregnancy and their clinical relevance. *Clin Pharmacokinet.* 1997;33(5):328-343.

21. Heikkinen T, Ekblad U, Laine K. Transplacental transfer of citalopram, fluoxetine and their primary demethylated metabolites in isolated perfused human placenta. *Bjog-an International Journal of Obstetrics and Gynaecology.* 2002;109(9):1003-1008.

22. Heikkinen T, Ekblad U, Laine K. Transplacental transfer of amitriptyline and nortriptyline in isolated perfused human placenta. *Psychopharmacology (Berl).* 2001;153(4):450-454.

23. Malek A, Mattison DR. Drugs and Medicines in Pregnancy: The Placental Disposition of Opioids. *Current Pharmaceutical Biotechnology.* 2011;12(5):797-803.

24. Loughhead AM, Fisher AD, Newport DJ, et al. Antidepressants in amniotic fluid: another route of fetal exposure. *The American journal of psychiatry.* 2006;163(1):145-147.

25. Hostetter A, Ritchie JC, Stowe ZN. Amniotic fluid and umbilical cord blood concentrations of antidepressants in three women. *Biol Psychiatry.* 2000;48(10):1032-1034.

26. Fokina VM, West H, Oncken C, et al. Bupropion therapy during pregnancy: the drug and its major metabolites in umbilical cord plasma and amniotic fluid. *Am J Obstet Gynecol.* 2016;215(4):497 e491-497.

27. Sit D, Perel JM, Wisniewski SR, Helsel JC, Luther JF, Wisner KL. Mother-infant antidepressant concentrations, maternal depression, and perinatal events. *J Clin Psychiatry.* 2011;72(7):994-1001.

28. Rampono J, Simmer K, Ilett KF, et al. Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry.* 2009;42(3):95-100.

29. Loughhead AM, Stowe ZN, Newport DJ, Ritchie JC, DeVane CL, Owens MJ. Placental passage of tricyclic antidepressants. *Biol Psychiatry.* 2006;59(3):287-290.

30. Rampono J, Proud S, Hackett LP, Kristensen JH, Ilett KF. A pilot study of newer antidepressant concentrations in cord and maternal serum and possible effects in the neonate. *Int J Neuropsychopharmacol.* 2004;7(3):329-334.

31. Hendrick V, Stowe ZN, Altshuler LL, Hwang S, Lee E, Haynes D. Placental passage of antidepressant medications. *The American journal of psychiatry.* 2003;160(5):993-996.

32. Huang H, Coleman S, Bridge JA, Yonkers K, Katon W. A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight. *Gen Hosp Psychiatry.* 2014;36(1):13-18.

33. Ross LE, Grigoriadis S, Mamisashvili L, et al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. *JAMA Psychiatry.* 2013;70(4):436-443.

34. Yazdy MM, Desai RJ, Brogly SB. Prescription Opioids in Pregnancy and Birth Outcomes: A Review of the Literature. *J Pediatr Genet.* 2015;4(2):56-70.

35. Morales DR, Slattery J, Evans S, Kurz X. Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: systematic review of observational studies and methodological considerations. *BMC Medicine.* 2018;16(1):6.

36. Bourke CH, Stowe ZN, Owens MJ. Prenatal antidepressant exposure: clinical and preclinical findings. *Pharmacol Rev.* 2014;66(2):435-465.

37. Naffah-Mazzacoratti MG, Rosenberg R, Fernandes MJ, et al. Serum serotonin levels of normal and autistic children. *Braz J Med Biol Res.* 1993;26(3):309-317.

38. Hranilovic D, Bujas-Petkovic Z, Vragovic R, Vuk T, Hock K, Jernej B. Hyperserotonemia in adults with autistic disorder. *Journal of autism and developmental disorders.* 2007;37(10):1934-1940.

39. Murphy DG, Daly E, Schmitz N, et al. Cortical serotonin 5-HT2A receptor binding and social communication in adults with Asperger's syndrome: an in vivo SPECT study. *The American journal of psychiatry.* 2006;163(5):934-936.

40. Yang CJ, Tan HP, Du YJ. The developmental disruptions of serotonin signaling may involved in autism during early brain development. *Neuroscience.* 2014;267:1-10.

41. Hadjikhani N. Serotonin, pregnancy and increased autism prevalence: is there a link? *Med Hypotheses.* 2010;74(5):880-883.

42. Chugani DC, Muzik O, Behen M, et al. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. *Ann Neurol.* 1999;45(3):287-295.

43. Chugani DC, Muzik O, Rothermel R, et al. Altered serotonin synthesis in the dentatothalamocortical pathway in autistic boys. *Ann Neurol.* 1997;42(4):666-669.

44. 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.

45. Viktorin A, Lichtenstein P, Lundholm C, et al. Selective serotonin re-uptake inhibitor use during pregnancy: association with offspring birth size and gestational age. *International Journal of Epidemiology.* 2016;45(1):170-177.

46. Pettersson E, Sjölander A, Almqvist C, et al. Birth weight as an independent predictor of ADHD symptoms: a within-twin pair analysis. *Journal of child psychology and psychiatry, and allied disciplines.* 2015;56(4):453-459.

47. Class QA, Rickert ME, Larsson H, Lichtenstein P, D'Onofrio BM. Fetal growth and psychiatric and socioeconomic problems: population-based sibling comparison. *Br J Psychiatry.* 2014;205(5):355-361.

48. D'Onofrio BM, Class QA, Rickert ME, Larsson H, Langstrom N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. *JAMA Psychiatry.* 2013;70(11):1231-1240.

49. Murray E, Pearson R, Fernandes M, et al. Are fetal growth impairment and preterm birth causally related to child attention problems and ADHD? Evidence from a comparison between high-income and middle-income cohorts. *J Epidemiol Community Health.* 2016;70(7):704-709.

50. Wong J, Motulsky A, Eguale T, Buckeridge DL, Abrahamowicz M, Tamblyn R. Treatment Indications for Antidepressants Prescribed in Primary Care in Quebec, Canada, 2006-2015. *JAMA.* 2016;315(20):2230-2232.

51. Kendler KS, Karkowski LM, Prescott CA. Causal Relationship Between Stressful Life Events and the Onset of Major Depression. *American Journal of Psychiatry.* 1999;156(6):837-841.

52. Pine DS, Cohen P, Johnson JG, Brook JS. Adolescent life events as predictors of adult depression. *J Affect Disord.* 2002;68(1):49-57.

53. Rai D, Lee BK, Dalman C, Golding J, Lewis G, Magnusson C. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. *BMJ.* 2013;346:f2059.

54. Class QA, Abel KM, Khashan AS, et al. Offspring psychopathology following preconception, prenatal and postnatal maternal bereavement stress. *Psychological medicine.* 2014;44(1):71-84.

55. O'Connor TG, Heron J, Golding J, Beveridge M, Glover V. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years - Report from the Avon Longitudinal Study of Parents and Children. *British Journal of Psychiatry.* 2002;180:502-508.

56. O'Connor TG, Heron J, Golding J, Glover V. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *Journal of child psychology and psychiatry, and allied disciplines.* 2003;44(7):1025-1036.

57. Van den Bergh BR, Marcoen A. High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. *Child Dev.* 2004;75(4):1085-1097.

58. Martini J, Knappe S, Beesdo-Baum K, Lieb R, Wittchen HU. Anxiety disorders before birth and self-perceived distress during pregnancy: associations with maternal depression

and obstetric, neonatal and early childhood outcomes. *Early Hum Dev.* 2010;86(5):305-310.

59. Grizenko N, Fortier ME, Gaudreau-Simard M, Jolicoeur C, Joober R. The effect of maternal stress during pregnancy on IQ and ADHD symptomatology. *J Can Acad Child Adolesc Psychiatry.* 2015;24(2):92-99.

60. Lovejoy MC, Graczyk PA, O'Hare E, Neuman G. Maternal depression and parenting behavior: a meta-analytic review. *Clin Psychol Rev.* 2000;20(5):561-592.

61. Ellis B, Nigg J. Parenting practices and attention-deficit/hyperactivity disorder: new findings suggest partial specificity of effects. *J Am Acad Child Adolesc Psychiatry.* 2009;48(2):146-154.

62. Bonari L, Pinto N, Ahn E, Einarson A, Steiner M, Koren G. Perinatal risks of untreated depression during pregnancy. *Can J Psychiatry.* 2004;49(11):726-735.

63. Lorant V, Deliege D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic inequalities in depression: a meta-analysis. *Am J Epidemiol.* 2003;157(2):98-112.

64. Chai WW, Fan JX, Wen M. Association of Individual and Neighborhood Factors with Home Food Availability: Evidence from the National Health and Nutrition Examination Survey. *Journal of the Academy of Nutrition and Dietetics.* 2018;118(5):815-823.

65. Ampaabeng SK, Tan CM. The long-term cognitive consequences of early childhood malnutrition: The case of famine in Ghana. *Journal of Health Economics.* 2013;32(6):1013-1027.

66. Galler JR, Bryce CP, Waber DP, et al. Infant malnutrition predicts conduct problems in adolescents. *Nutritional neuroscience.* 2012;15(4):186-192.

67. Galler JR, Bryce CP, Zichlin ML, Fitzmaurice G, Eaglesfield GD, Waber DP. Infant malnutrition is associated with persisting attention deficits in middle adulthood. *The Journal of nutrition.* 2012;142(4):788-794.

68. Solovieff N, Cotsapas C, Lee PH, Purcell SM, Smoller JW. Pleiotropy in complex traits: challenges and strategies. *Nature reviews Genetics.* 2013;14(7):483-495.

69. Scherff A, Taylor M, Eley TC, Happe F, Charman T, Ronald A. What causes internalising traits and autistic traits to co-occur in adolescence? A community-based twin study. *J Abnorm Child Psychol.* 2014;42(4):601-610.

70. Cole J, Ball HA, Martin NC, Scourfield J, McGuffin P. Genetic overlap between measures of hyperactivity/inattention and mood in children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 2009;48(11):1094-1101.

71. Lee SH, Ripke S, Neale BM, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics.* 2013;45(9):984-+.

72. Illamola SM, Bucci-Rechtweg C, Costantine MM, Tsilou E, Sherwin CM, Zajicek A. Inclusion of pregnant and breastfeeding women in research - efforts and initiatives. *Br J Clin Pharmacol.* 2018;84(2):215-222.

73. Thoemmes F, Ong AD. A Primer on Inverse Probability of Treatment Weighting and Marginal Structural Models. *Emerging Adulthood.* 2015;4(1):40-59.

74. Boukhris T, Sheehy O, Mottron L, Berard A. Antidepressant Use During Pregnancy and the Risk of Autism Spectrum Disorder in Children. *JAMA Pediatr.* 2016;170(2):117-124.

75. El Marroun H, White TJ, van der Knaap NJ, et al. Prenatal exposure to selective serotonin reuptake inhibitors and social responsiveness symptoms of autism: population-based study of young children. *Br J Psychiatry.* 2014;205(2):95-102.

76. Harrington RA, Lee LC, Crum RM, Zimmerman AW, Hertz-Picciotto I. Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. *Pediatrics.* 2014;133(5):e1241-1248.

77. 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.

78. Rai D, Lee BK, Dalman C, Newschaffer C, Lewis G, Magnusson C. Antidepressants during pregnancy and autism in offspring: population based cohort study. *BMJ.* 2017;358.

79. Sorensen MJ, Gronborg TK, Christensen J, et al. Antidepressant exposure in pregnancy and risk of autism spectrum disorders. *Clin Epidemiol.* 2013;5:449-459.

80. Viktorin A, Uher R, Reichenberg A, Levine SZ, Sandin S. Autism risk following antidepressant medication during pregnancy. *Psychological Medicine.* 2017:1-10.

81. Academy of Medical Sciences Working Group. *Identifying the environmental causes of disease: How should we decide what to believe and when to take action?* London: Academy of Medical Sciences; 2007.

82. Westfall J, Yarkoni T. Statistically Controlling for Confounding Constructs Is Harder than You Think. *PLoS ONE.* 2016;11(3):e0152719.

83. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: A tool for detecting confounding and bias in observational studies. *Epidemiology.* 2010;21(3):383-388.

84. Richmond RC, Al-Amin A, Smith GD, Relton CL. Approaches for drawing causal inferences from epidemiological birth cohorts: a review. *Early Hum Dev.* 2014;90(11):769-780.

85. Smith GD. Assessing Intrauterine Influences on Offspring Health Outcomes: Can Epidemiological Studies Yield Robust Findings? *Basic & Clinical Pharmacology & Toxicology.* 2008;102(2):245-256.

86. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: Historical foundations and contemporary application. *Current Epidemiology Reports.* 2015;2(4):221-228.

87. Ray WA, Griffin MR. Use of medicaid data for pharmacoepidmiology. *American Journal of Epidemiology.* 1989;129(4):837-849.

88. D'Onofrio BM, Lahey BB, Turkheimer E, Lichtenstein P. The critical need for family-based, quasi-experimental research in integrating genetic and social science research. *American Journal of Public Health.* 2013;103:S46-S55.

89. Lahey BB, D'Onofrio BM. All in the Family: Comparing Siblings to Test Causal Hypotheses Regarding Environmental Influences on Behavior. *Current Directions in Psychological Science.* 2010;19(5):319-323.

90. Frisell T, Oberg S, Kuja-Halkola R, Sjolander A. Sibling comparison designs: bias from non-shared confounders and measurement error. *Epidemiology.* 2012;23(5):713-720.

91. Sjölander A, Zetterqvist J. Confounders, Mediators, or Colliders: What Types of Shared Covariates Does a Sibling Comparison Design Control For? *Epidemiology.* 2017;28(4):540-547.

92. 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.

93. Sujan AC, Quinn PD, Rickert ME, et al. Maternal prescribed opioid analgesic use during pregnancy and associations with adverse birth outcomes: A population-based study. *PLOS Medicine.* 2019;16(12):e1002980.

94. Sujan AC, Rickert ME, Quinn PD, et al. Concurrent prescriptions of opioid analgesic and selective-serotonin reuptake inhibitor medications during pregnancy and risk for adverse birth outcomes: A population-based study using inverse probability of treatment weighting. under review.

95. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European journal of epidemiology.* 2009;24(11):659-667.

96. Miettunen J, Suvisaari J, Haukka J, Isohanni M. Use of register data for psychiatric epidemiology in the Nordic countries. In: Tsuang MT, Tohen M, Jones P, eds. *Textbook of Psychiatric Epidemiology.* 3rd ed. Chichester, UK: Wiley; 2011:117-131.

97. Byrne N, Regan C, Howard L. Administrative registers in psychiatric research: a systematic review of validity studies. *Acta Psychiatrica Scandinavica.* 2005;112:409-414.

98. National Board of Health and Welfare. *The Swedish Medical Birth Register - A Summary of Content and Quality.* Stockholm: National Board of Health and Welfare;2003.

99. Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. *Scand J Soc Med.* 1990;18(2):143-148.

100. National Board of Health and Welfare. *Pregnancies, Deliveries and Newborn Infants - The Swedish Medical Birth Register 1973-2011, Assisted Reproduction, treatment 1991-2010 [in Swedish].* Stockholm2013.

101. Statistics Sweden. *Multi-Generation Register 2009 - A Description of Contents and Quality.* Örebro, Sweden2010.

102. National Board of Health and Welfare. *Quality and Content in the Patient Register - Inpatient care discharges 1964-2007 and outpatient (specialized care) visits 1997-2007 [in Swedish].* Stockholm: National Board of Health and Welfare;2009. 2009-125-15.

103. WHO. *International Classification of Diseases, World Health Organization WHO.* Geneva1992.

104. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health.* 2011;11:450.

105. National Board of Health and Welfare. *4 years with the Prescribed Drug Register [in Swedish].* Stockholm: National Board of Health and Welfare;2010.

106. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiology and drug safety.* 2007;16(7):726-735.

107. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC classification and DDD assignment 2013.* Oslo: WHO Collaborating Centre for Drug Statistics Methodology;2012.

108. International Narcotics Control Board. Narcotic Drugs 2017: Estimated world requirements for 2018, Statistics for 2016. In. New York 2018.

109. Statistics Sweden. *Multi-generation register 2005 – A description of contents and quality.* Örebro: Statistics Sweden;2006. 2006:6.

110. Statistics Sweden. Education in Sweden 2009. . https://www.scb.se/statistik/_publikationer/UF0527_2009A01_BR_UF08BR0901.pdf. Published 2009. Updated February 21, 2014. Accessed.

111. LISA database. http://www.scb.se/Pages/List____257743.aspx. Accessed.

112. Statistics_Sweden_Regional_Registry. http://www.scb.se/Regionalt. Accessed.

113. Fazel S, Grann M. The population impact of severe mental illness on violent crime. *Am J Psychiatry.* 2006;163(8):1397-1403.

114. BRÅ e. Kriminalstatistik 2010 [Criminal statistics]. . In: Västerås, ed2011.

115. Magnusson PKE, Gunnell D, Tynelius P, Smith GD, Rasmussen F. Strong inverse association between height and suicide in a large cohort of Swedish men: Evidence of early life origins of suicidal behavior? *American Journal of Psychiatry.* 2005;162:1373.

116. Lichtenstein P, Sullivan PF, Cnattingius S, et al. The Swedish Twin Registry in the third millennium: an update. *Twin research and human genetics : the official journal of the International Society for Twin Studies.* 2006;9(6):875-882.

II. Paper 1:

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.

Citation:

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Abstract

Importance: Prenatal antidepressant exposure has been associated with adverse outcomes. Previous studies, however, may not have adequately accounted for confounding.

Objective: To evaluate alternative hypotheses for associations between first-trimester antidepressant exposure and birth and neurodevelopmental problems.

Design, Setting, and Participants: This retrospective cohort study included Swedish offspring born between 1996 and 2012 and followed through 2013 or censored by death or emigration. Analyses controlling for pregnancy, maternal, and paternal covariates, as well as sibling comparisons, timing of exposure comparisons, and paternal comparisons, were used to examine the associations.

Exposures: Maternal self-reported first-trimester antidepressant use and first-trimester antidepressant dispensations.

Main Outcomes and Measures: Preterm birth (< 37 gestational weeks), small for gestation age (birth weight more than 2 standard deviations below the expected weight for gestational age), and first inpatient or outpatient clinical diagnosis of autism spectrum disorder and attention-deficit/hyperactivity disorder in offspring.

Results: Among 1,580,629 offspring (mean gestational age 279 days; 48.6% female; 1.4% [n=22,544] with maternal first-trimester self-reported antidepressant use) born to 943,776 mothers (mean age at childbirth 30 years), 7.0% of exposed vs. 4.8% of unexposed offspring were preterm, 2.5% of exposed vs. 2.2% of unexposed were small for gestational age, 5.3% of exposed vs. 2.1% of unexposed were diagnosed with autism spectrum disorder by age 15, and 12.6% of exposed vs. 5.5% of unexposed were diagnosed by attention-deficit/hyperactivity disorder by age 15. At the population level, first-trimester exposure was associated with all

outcomes, compared with unexposed offspring (preterm birth: OR=1.5, 95% CI, [1.4, 1.6]; small for gestational age: OR=1.2, 95% CI, [1.1, 1.3]; autism spectrum disorder: HR=2.0, 95% CI, [1.8, 2.3]; attention-deficit/hyperactivity disorder: HR=2.2, 95% CI, [2.0, 2.4]). However, in models that compared siblings while adjusting for pregnancy, maternal, and paternal traits, first-trimester antidepressant exposure was associated with preterm birth (OR = 1.3, 95% CI [1.2, 1.5]) but not with small for gestational age (OR = 1.0, 95% CI [0.8, 1.3]), autism spectrum disorder (HR = 0.8, 95% CI [0.6, 1.1]), or attention-deficit/hyperactivity disorder (HR = 1.0, 95% CI [0.8, 1.3]). Results from analyses assessing associations with maternal dispensations before pregnancy and paternal first-trimester dispensations were consistent with findings from the sibling comparisons.

Conclusion and Relevance: Among offspring born in Sweden, after accounting for confounding factors, first-trimester antidepressant exposure, compared to no exposure, was associated with a small increased risk of preterm birth but no increased risk of small for gestational age, autism spectrum disorder, or attention-deficit/hyperactivity disorder.

Introduction

Given the increasing prevalence of antidepressant use among pregnant women,[1] gaining knowledge on the safety of their use during pregnancy is a public health priority. Prenatal antidepressant exposure is associated with birth and neurodevelopmental problems, including shorter gestation,[2] reduced fetal growth,[2] autism spectrum disorder,[3-6] and attention-deficit/hyperactivity disorder.[7] These associations may be due to causal mechanisms (e.g., dysfunctional serotonin signaling[8]). However, there are alternative explanations for the associations. Maternal depression and stress are associated with birth[9] and neurodevelopmental[10] problems, suggesting that antidepressant associations could be attributable to confounding by indication for such treatment. Furthermore, autism spectrum disorder and attention-deficit/hyperactivity disorder have strong genetic influences,[11] and these influences partially overlap with genetic contributions to depression.[12,13] Thus, genetic transmission of shared risk for neurodevelopmental problems and depression could explain the associations (i.e., passive gene-environmental correlation). Other factors, such as poor health practices during pregnancy, could also account for the associations.[14]

Randomized clinical trials have not been able to test the safety of antidepressant use during pregnancy because pregnant women are typically excluded from these studies. Thus, researchers must use observational designs to rule out alternative explanations for the associations.[15] The present study used four such designs to explore associations between first-trimester antidepressant exposure (assessed via both maternal self-report and registered medication dispensations) and offspring birth and neurodevelopmental problem (i.e., preterm birth, small for gestational age, autism spectrum disorder, and attention-deficit/hyperactivity disorder. In addition to (1) statistical controls to adjust for measured pregnancy, maternal, and

paternal characteristics, this study used (2) sibling comparisons to account for unmeasured genetic and environmental factors that make siblings similar, (3) timing-of-exposure comparisons to account for selection factors related to maternal antidepressant treatment around the time of pregnancy, and (4) paternal comparisons to further account for familial confounding.

Methods

The institutional review board at Indiana University and the Regional Ethical Review Board in Stockholm approved this study. By Swedish law informed consent was not necessary because the study used data available from national registers.

Sample

We obtained a population-based dataset by linking information from the following Swedish registers: (1) the Multi-Generation Register, which included biological relationships for all individuals residing in Sweden since 1961, (2) the Prescribed Drug Register, which included prescription medication dispensation records since 2006, (3) the Medical Birth Register, which included information on 96-99% of births since 1973, (4) the National Patient Register, which included diagnoses from all hospital admissions since 1987 and specialist outpatient care since 2001, (5) the National Crime Register, which included criminal convictions since 1973, and (6) the Education Register, which included highest level of completed formal education through 2013.

Measures

Antidepressant exposure. The main exposures evaluated were first-trimester exposure to (1) any antidepressants (medications with Anatomical Therapeutic Chemical Classification [ATC] codes beginning with N06A) and (2) Selective Serotonin Reuptake Inhibitors (SSRIs; medications with ATC codes beginning with N06AB). Exposure was defined according to two

sources of information: (1) maternal self-reports (available for offspring born between 1996 and 2012) and (2) dispensation records (available for both parents of offspring born between 2006 and 2012).

Information on maternal *self-reported* medication use during the first trimester of pregnancy came from the Medical Birth Register, which contains information obtained from standardized interviews conducted by midwives at the first antenatal visit. Medication reported in these interviewers is presumed to represent first-trimester use because interviews typically occur between week 10 and 12 of pregnancy.

Information on medication use based on *dispensation* records came from the Prescribed Drug Register, which covers all medication dispensations and accompanying prescriptions made in Sweden since July 2005. The only medication use not covered by the register is medication administered while in hospital, purchased over the counter, or obtained on the black market. The Prescribed Drug Register was used to obtain information on *maternal* antidepressant dispensations that covered the periods before pregnancy and during the first trimester of pregnancy and *paternal* antidepressants that covered the period during the first trimester of pregnancy. First-trimester exposure was defined as having at least one dispensation between 90 days before estimated conception and 90 days after estimated conception (see sFigure II.1). The window included 90 days before conception because chronic disease medication is typically prescribed for at least 3-month periods in Sweden. Use before pregnancy only was defined as having at least one dispensation between 270 and 90 days before estimated conception and no dispensations during pregnancy or during the 180 days after delivery.

Main Outcomes. The birth outcomes were preterm birth (< 37 gestational weeks) and small for gestational age (birth weight more than 2 standard deviations below the expected

weight for gestational age). The neurodevelopmental outcomes were first diagnosis of autism spectrum disorder and attention-deficit/hyperactivity disorder, which were identified using inpatient and outpatient diagnoses made by specialists according to *International Classification of Diseases, Ninth Revision* (ICD-9) and ICD-10 criteria. Previous research has validated these diagnoses in the Swedish registers.[16,17] Participants were followed through 2013 or were censored because of death or emigration. More details about the registers and variables are available in previous publications.[e.g.,18,19]

Covariates. Pregnancy covariates included parity (categorized as first, second, third, or fourth or higher) and year of birth. Maternal and paternal covariates included country of birth (Sweden or outside Sweden), age at childbearing (categorized into six levels), highest level of completed education (categorized into seven levels), history of any criminal conviction, history of severe psychiatric problems (inpatient diagnosis of ICD-8, ICD-9, or ICD-10 schizophrenia, bipolar disorder, or other non-drug-induced psychoses), and history of any suicide attempts (definite or uncertain). History of criminal convictions is commonly used in Swedish register studies to index problems with behavior regulation.[e.g.,20,21]

Analyses

We performed a complete-case analysis. We managed and analyzed data in SAS 9.4 and STATA 13.1 and calculated 95% confidence intervals based on two-sided hypothesis testing.

Descriptive statistics. We provided the distribution of covariates and outcomes in the whole sample and in the subsamples of exposed an unexposed offspring. In addition, we provided the occurrence of the outcomes and covariates in differentially exposed and unexposed siblings. For the birth outcomes, we presented proportions and unadjusted risk differences. We

presented Kaplan Meier estimates of the probability of the neurodevelopmental diagnoses because follow-up time was censored.

Population-wide associations and within-family comparisons. Logistic regression was used to estimate the model-based associations for the two birth (i.e., binary response) outcomes. Cox proportional hazards regression (using calendar age in years as the timescale) was used to estimate the associations for the two neurodevelopmental outcomes to account for censored observations in the data. We examined the associations between antidepressant exposure and outcomes by estimating a sequence of three models with increasing degree of control for potential confounding factors. First, the baseline models assessed population-wide associations while only adjusting for pregnancy covariates (parity and year of birth). Second, the population-wide associations were further adjusted for all maternal and paternal covariates. These population models used robust standard errors to account for clustering of individuals (i.e., siblings) within nuclear families bound by the same biological mother. Third, sibling comparison models compared exposure and outcome discordant offspring within families and included covariates that could vary among siblings born to the same mother. By design, these models accounted for all factors that made siblings similar (e.g., shared genetic and early environmental influences), as well as measured covariates that vary within families, thereby producing a stronger test of the associations than the adjusted population models.[22] As recommended,[23] we fit fixed-effects models using conditional logistic and stratified Cox regression to make purely within-family comparisons.

Comparisons of timing of maternal use and paternal use. To explore whether intrauterine exposure was specifically associated with outcomes over and above maternal depression treatment around the time of pregnancy, we compared associations for maternal first-

trimester antidepressant dispensations with associations for dispensations before pregnancy, while adjusting for measured pregnancy, maternal, and paternal covariates. We evaluated whether these associations differed statistically using Wald χ^2 tests. We also compared the fit of models that included separate parameters for before pregnancy dispensations and first-trimester dispensations to models that included one parameter for both dispensation windows. In addition, paternal first-trimester antidepressant dispensations were used as a negative control to further explore the role of familial confounding. We first assessed the association between maternal and paternal first-trimester dispensations. We then estimated associations between paternal first-trimester antidepressant dispensations and the four outcomes while adjusting for the pregnancy covariates.

Sensitivity analyses. First, to evaluate the influence of exposure misclassification, we examined adjusted associations with five additional exposure definitions in the cohort with exposure information from both maternal self-reports and dispensations (i.e., the cohort born 2006 to 2012). The four additional definitions included: (a) first-trimester exposure defined as use according to *either* self-reports or dispensation records, (b) first-trimester exposure defined as use according to *both* self-reports and dispensation records, (c) a narrower first-trimester dispensation window of 30 days before conception to 90 days after conception, and (d) at least two dispensations during the original first-trimester exposure window. Second, given that single-offspring families cannot contribute to sibling-comparison analyses, we reassessed the population models in the subsample of offspring with siblings to evaluate the generalizability of sibling-comparison results. Third, to assess if exposure to other psychotropic medications confounded the associations, we restricted the analyses to offspring not exposed to other psychotropic medications. Fourth, given that prior to 2001 outpatient psychiatric diagnoses were

not included in the National Patient Register, we conducted analyses on a subsample of offspring born after 2000 to assess whether left censoring of the neurodevelopmental outcomes biased the findings. These analyses also enabled us to explore whether cohort effects influenced the results. Fifth, we estimated the associations with the neurodevelopmental outcomes in subsamples excluding offspring with diagnoses before age 2 to address concerns about the validity of early neurodevelopmental diagnoses. Sixth, because the main analyses focused on first-trimester exposure, we examined the association between dispensations during the second and/or third trimester and each outcome in the subsample of offspring whose mothers had a dispensation during the first trimester.

Results

The target sample included 1,670,237 offspring born 1996-2012. Multiple births (48,979 offspring), cases with missing father identifier (16,295), missing or invalid responses on covariates (20,118), and missing on the small for gestational age variable (4,216) were sequentially dropped. The final analytic cohort of 1,580,629 offspring (48.6% female) represented 95% of target singleton births and included 943,776 distinct mothers and 946,579 distinct fathers. According to maternal self-reports, 22,544 (1.4%) of the offspring in the final cohort were exposed to any antidepressant during the first trimester, and of these, 82% (18,470) were exposed to SSRIs.

The timing of exposure and paternal comparisons were conducted on the subsample of 708,450 offspring (born between 2006 and 2012) with dispensation-based exposure data. There were 26,477 (3.7%) offspring with first-trimester maternal antidepressant dispensations. Of these, 84% (22,125) had first-trimester maternal SSRI dispensations specifically. There were 8,203 (1.2%) offspring who had mothers with antidepressant dispensations before pregnancy

only. Of these, 81% (6,674) had mothers who were specifically dispensed SSRIs before pregnancy. There were 18,727 (2.6%) offspring who had fathers with first-trimester antidepressant dispensations. Of these, 72% (13,521) had fathers with first-trimester SSRI dispensations specifically.

The same pattern of results was observed for associations with first-trimester exposure to any antidepressant as first-trimester exposure to SSRIs specifically. Therefore, results for exposure to any antidepressant are presented in the text and tables. The results for SSRIs can be found in the tables and online supplement.

Descriptive Statistics Stratified by Maternal Self-reported Antidepressant Use

In the whole sample, 7.0% of exposed and 4.8% of unexposed offspring were preterm (Table II.1), which equates to 220 (95% CI [187, 254]) additional preterm birth cases per 10,000 offspring. Approximately 2.5% of exposed and 2.2% of unexposed offspring were born small for gestational age, (risk difference=35 additional cases per 10,000 offspring; 95% CI [14, 56]). Compared to unexposed offspring, exposed offspring also had a higher probability of the neurodevelopmental diagnoses (see Figure II.1a and 1c for the Kaplan Meier estimates and confidence intervals). For example, by age 15, Kaplan Meier estimates indicated a cumulative risk of autism spectrum disorder of 5.3% for exposed and 2.1% for unexposed offspring. By age 15, the cumulative risk of attention-deficit/hyperactivity disorder was 12.6% for exposed and 5.5% for unexposed offspring. See SII.1 Appendix for more descriptive information.

Among differentially exposed siblings, 6.2% of exposed and 5.1% of unexposed siblings were born preterm. However, 1.9% of exposed and 2.0% of unexposed siblings were small for gestational age. See Figure II.1b and 1d for the probabilities of the neurodevelopmental diagnoses among differentially exposed siblings through age 15. By age 15, the cumulative risk

for autism spectrum disorder was 5.5% for exposed and 4.6% for unexposed siblings; the cumulative risk for attention-deficit/hyperactivity disorder was 12.4% for exposed and 12.7% for unexposed siblings.

Population-wide Associations and Sibling Comparisons

In the baseline models (Table II.2), maternal self-reported first-trimester antidepressant use was associated with preterm birth (OR = 1.5, 95% CI [1.4, 1.6]), small for gestational age (OR = 1.2, 95% CI [1.1, 1.3]), autism spectrum disorder (HR = 2.0, 95% CI [1.8, 2.3]), and attention-deficit/hyperactivity disorder (HR = 2.2, 95% CI [2.0, 2.4]). In the adjusted models, first-trimester exposure to antidepressants was also statistically significantly associated with all outcomes (preterm birth OR = 1.4, 95% CI [1.3, 1.4]; small for gestational age OR = 1.1, 95% CI [1.0, 1.2]; autism spectrum disorder HR = 1.6, 95% CI [1.5, 1.8]; attention-deficit/hyperactivity disorder HR = 1.6, 95% CI [1.5, 1.7]).

In the sibling comparison models, first-trimester exposure was associated with preterm birth (OR = 1.3, 95% CI [1.2, 1.5], $p < 0.0001$). However, it was not associated with small for gestational age (OR = 1.0, 95% CI [0.8, 1.3]), autism spectrum disorder (HR = 0.8, 95% CI [0.6, 1.1]), or attention-deficit/hyperactivity disorder (HR = 1.0, 95% CI [0.8, 1.3]). See SII.1 Appendix for information on offspring who could contribute to sibling comparison analyses.

Comparisons of Timing of Maternal Use and Paternal Use

Dispensation data was used in timing of exposure and paternal comparisons (see SII.2 Appendix for more information). For preterm birth, the association with maternal dispensations before pregnancy but not during or after pregnancy (OR=1.2, 95% CI [1.1, 1.3]; Table II.3) was statistically significantly weaker than the association with first-trimester maternal dispensations (OR=1.4, 95% CI [1.3, 1.5]). For all other outcomes, the associations with maternal

dispensations before but not during or after pregnancy did not statistically significantly differ from the associations with first-trimester maternal dispensations.

Paternal first-trimester antidepressant dispensations were associated with maternal first-trimester antidepressant dispensations (OR=3.4, 95% CI [3.3, 3.6]). Paternal first-trimester antidepressant dispensations (Table II.4) had very modest associations with preterm birth (OR=1.1, 95% CI [1.1, 1.2]) and small for gestational age (OR=1.1, 95% CI [1.0, 1.2]), with the latter not being statistically significant. Paternal dispensations during pregnancy were associated with autism spectrum disorder (HR=1.3, 95% CI [1.1, 1.6]), and attention-deficit/hyperactivity disorder (HR=1.7, 95% CI [1.4, 2.2]).

Sensitivity Analyses

Sensitivity analyses showed a consistent pattern of results across analyses using stricter criteria for exposure and narrower exposure windows, suggesting that exposure misclassification was not responsible for the pattern of findings (SII.3 Appendix). Results from population models conducted on a subsample that excluded offspring who did not have siblings also were essentially identical to the main results (SII.4 Appendix). These results provide support for the generalizability of sibling comparison results. Sensitivity analyses also suggested that confounding by exposure to other psychotropic medications (SII.5 Appendix); left censoring of the neurodevelopmental outcomes and cohort effects (SII.6 Appendix); and measurement error of the neurodevelopmental outcomes (SII.7 Appendix) had very little influence on the results. In addition, among offspring whose mothers had a dispensation during the first trimester, a dispensation during the second or third trimester was associated with increased risk of the pregnancy outcomes, though the associations with the neurodevelopmental diagnoses were not statistically significant (SII.8 Appendix).

Discussion

The present study found that, after accounting for measured pregnancy, maternal, and paternal traits, as well as all (unmeasured) stable familial characteristics shared by siblings, maternal antidepressant use during the first trimester of pregnancy, compared to no exposure, was associated with a small increased risk of preterm birth but no increased risk of small for gestational age, autism spectrum disorder, or attention-deficit/hyperactivity disorder. That is, unexposed siblings were at equal risk for small for gestational age, autism spectrum disorder, and attention-deficit/hyperactivity disorder as their exposed siblings. These results are consistent with the hypothesis that genetic and/or familial environmental factors account for the population-wide associations between first-trimester antidepressant exposure and these outcomes. Moreover, results from analyses examining timing of exposure were consistent with the interpretation of the sibling-comparison findings. Specifically, the strength of the associations between antidepressant dispensations before pregnancy and small for gestational age, autism spectrum disorder, and attention-deficit/hyperactivity disorder did not statistically significantly differ from that of associations for first-trimester antidepressant dispensations, suggesting that the underlying condition, rather than exposure to antidepressants during the first trimester, explained the associations. Paternal first-trimester antidepressant dispensations were also associated with the neurodevelopmental disorders. Because paternal antidepressant use during the first trimester is unlikely to contribute to intrauterine exposure, these findings provide further support that associations between first-trimester antidepressant exposure and offspring neurodevelopmental problems may, at least partially, be explained by familial confounding.

The results also showed that, across multiple designs that account for familial confounding factors, first-trimester antidepressant exposure was associated with a slightly

elevated risk of preterm birth. Although these results may be consistent with the hypothesis that prenatal antidepressant exposure could lead to a small increased risk of preterm birth, other possible explanations for the findings need to be considered. Most important, the potential role of confounding by maternal depression should be noted because both the existence and severity of depression symptoms in the mother could potentially influence the risk of preterm birth.[24]

The results of the population-wide models were consistent with numerous observational studies that have demonstrated associations between prenatal antidepressant exposure and birth and neurodevelopmental problems.[2-7] The results of the sibling comparisons were also consistent with the limited previous sibling-comparisons studies that have examined associations between prenatal antidepressant exposure and birth and neurodevelopmental problems. A sibling comparison study using dispensation data from the Swedish registers found a statistically significant associations between prenatal antidepressant dispensations and shorter gestation.[25] Another sibling comparison reported that prenatal antidepressant exposure was not associated with autism spectrum disorder,[26] although confidence intervals were too wide to draw strong conclusions.

The current study had several strengths. First, the study analyzed a large, population-based sample, which provided statistical power to examine rare-yet-serious outcomes. Second, the conclusions were based on converging evidence from multiple research designs that accounted for both measured and unmeasured confounding factors. Third, first-trimester antidepressant use was indexed by both maternal self-report and dispensations. Fourth, the study included four outcomes, two pregnancy-related and two neurodevelopmental problems, all of which are associated with significant morbidity and mortality. Fifth, sensitivity analyses suggested that misclassification of antidepressant use, several assumptions of sibling-comparison

analyses, confounding by other psychotropic medications, and misclassification of the neurodevelopmental problems were unlikely to influence the overall conclusions.

The findings from the present study should be considered in light of several limitations. First, and most important, observational designs such as these cannot fully rule out all sources of confounding. In particular, like other register-based approaches,[26] this study could not comprehensively assess maternal depression or its severity,[27] nor could it compare different antidepressant treatment regimes. Thus, associations could have been influenced by confounding by antidepressant indication. In order to address this limitation, the study used multiple designs, each of which could help rule out some but not all sources of confounding, to provide complementary evidence. For example, sibling comparisons ruled out all stable confounders (e.g., chronic maternal depression), but that design may not have been able to account for confounding from maternal depression that varied across pregnancies.[28] Thus, the within-family associations with preterm birth may plausibly be driven by unmeasured time-varying maternal depression rather than by antidepressant use.[29]

Second, this study focused on first-trimester exposure. Whereas one recent study found an association between antidepressant dispensations late—but not early—in pregnancy and autism spectrum disorder,[3] there has been considerable debate regarding the role of timing.[30-32] In fact, several studies have found stronger associations with first-trimester antidepressant use than with use later in pregnancy.[4,6] Supplemental analyses indicated that among offspring whose mothers had a dispensation during the first trimester, a dispensation during the second or third trimester was associated with greater risk of offspring being born preterm and small for gestational age. These associations could be due to intrauterine exposure to antidepressants later in pregnancy, increased severity of depression (i.e., confounding by indication), or other

unmeasured confounding. Future studies are, therefore, needed to explicitly examine whether timing of exposure moderates the preterm birth association or whether exposure later in pregnancy is more strongly associated with other outcomes.

Third, the vast majority of antidepressant exposure (82% according to maternal reports) was to SSRIs. Future research should explore class- and drug-specific associations. Fourth, analyses were conducted on a Swedish sample, and it is not known if results would generalize to other countries. Although the population-wide associations in the present study were commensurate with those from other countries, future research should use designs that help account for unmeasured confounders to explore associations with prenatal antidepressant exposure in the United States and elsewhere. Fifth, sibling comparisons require large samples to have adequate statistical power.[33] Although the large Swedish sample ensured fairly precise parameter estimates in sibling comparisons, small effects of antidepressant exposure cannot be ruled out. However, their magnitudes, particularly for the neurodevelopmental outcomes, would be much smaller than those suggested by population-wide associations.

Conclusion

Among offspring born in Sweden, after accounting for confounding factors, first-trimester exposure to antidepressants, compared to no exposure, was associated with a small increased risk of preterm birth but no increased risk of small for gestational age, autism spectrum disorder, or attention-deficit/hyperactivity disorder.

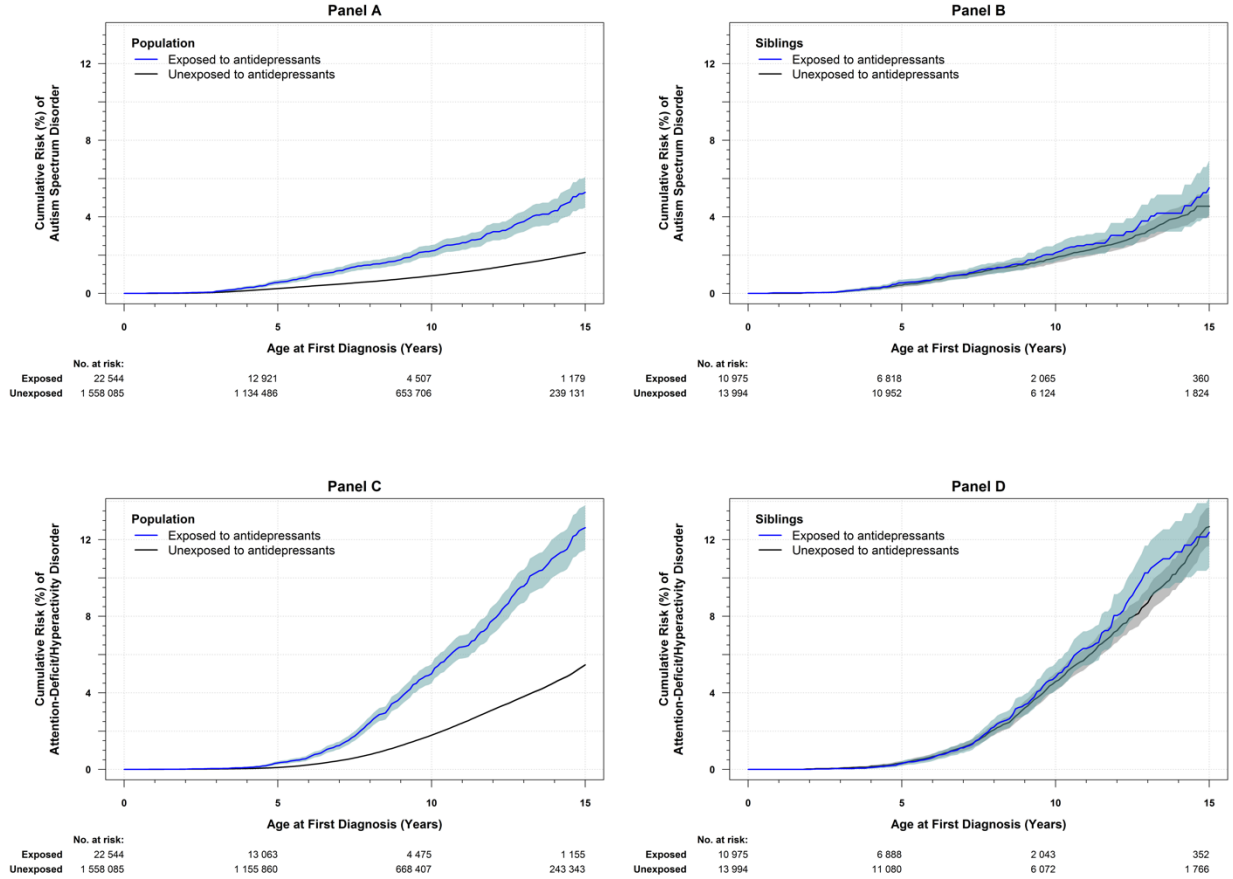


Figure II.1. Risk of Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder by Maternal Self-reported First-trimester Exposure. The figure shows Kaplan-Meier estimates of cumulative risk (i.e., proportion diagnosed with) the neurodevelopmental outcomes (y-axis) by age (x-axis) among offspring with and without maternal self-reported first-trimester antidepressant exposure. The blue line shows exposed offspring. The black line shows unexposed offspring. Shaded areas around the blue and black lines are pointwise 95% confidence intervals. Top panels (A and B) show risk for autism spectrum disorder. Bottom panels (C and D) show risk for attention-deficit/hyperactivity disorder. Left panels (A and C) include the full cohort. Right panels (B and D) include siblings discordant for first-trimester antidepressant exposure. The median and interquartile range (IQR) follow-up time in the study (i.e., age since birth in years) were estimated separately for each exposure group. The median follow-up for autism spectrum disorder in the full cohort was 8.71 y [IQR: (4.69, 13.19)] for the unexposed group, and 5.82 y [IQR: (3.32, 9.08)] for the exposed group. The median follow-up for autism spectrum disorder in the sample of discordant siblings was 9.24 y [IQR: (5.54, 12.96)] for the unexposed group, and 6.27 y [IQR: (3.77, 9.02)] for the exposed group. The median follow-up for attention-deficit/hyperactivity disorder in the full cohort was 8.54 y [IQR: (4.54, 13.54)] for the unexposed group, and 5.54 y [IQR: (3.54, 9.54)] for the exposed group. The median follow-up for attention-deficit/hyperactivity disorder in the sample of discordant siblings was 9.54 y [IQR: (5.54, 13.54)] for the unexposed group, and 6.54 y [IQR: (3.54, 9.54)] for the exposed group.

Table II.1. Descriptive statistics in the whole sample and stratified by maternal self-reported first-trimester use of any antidepressant

	Whole sample (n=1,580,629)	**Exposed offspring** (n=22,544)	**Unexposed offspring** (n=1,558,085)
	No. (%)	**No. (%)**	**No. (%)**
Offspring outcomes			
Preterm birth	76061 (4.81)	1574 (6.98)	74487 (4.78)
Small for gestational age	34728 (2.20)	573 (2.54)	34155 (2.19)
Autism spectrum disorder[a]	14617 (2.16)	299 (5.28)	14318(2.14)
Attention-deficit/hyperactivity disorder[a]	32924 (5.51)	613 (12.63)	32311(5.46)
Pregnancy covariates			
First born	693070 (43.85)	10467 (46.43)	682603 (43.81)
Second born	585619 (37.05)	6891 (30.57)	578728 (37.14)
Third born	213382 (13.50)	3463 (15.36)	209919 (13.47)
Fourth born or higher	88558 (5.60)	1723 (7.64)	86835 (5.57)
Born 1996 to 1999[b]	333791 (21.12)	1649 (7.31)	332142 (21.32)
Born 2000 to 2003[b]	349143 (22.09)	3004 (13.33)	346139 (22.22)
Born 2004 to 2007[b]	386511 (24.45)	6349 (28.16)	380162 (24.40)
Born 2008 to 2012[b]	511184 (32.34)	11542 (51.20)	499642 (32.07)
Maternal covariates			
Age at birth			
< 20 years	25637 (1.62)	327 (1.45)	25310 (1.62)
20 to 24 years	210552 (13.32)	2636 (11.69)	207916 (13.34)
25 to 29 years	495050 (31.32)	6124 (27.16)	488926 (31.38)
30 to 34 years	544746 (34.46)	7599 (33.71)	537147 (34.47)
35 to 39 years	254771 (16.12)	4730 (20.98)	250041 (16.05)
≥ 40 years	49873 (3.16)	1128 (5.00)	48745 (3.13)
Education			
Primary and lower secondary, < 9 years	33648 (2.13)	180 (0.80)	33468 (2.15)
Primary and lower secondary, 9 years	107953 (6.83)	2684 (11.91)	105269 (6.76)
Upper secondary, 1-2 years	246415 (15.59)	3852 (17.09)	242563 (15.57)
Upper secondary, 3 years	414949 (26.25)	6053 (26.85)	408896 (26.24)
Post-secondary, < 3 years	224706 (14.22)	3012 (13.36)	221694 (14.23)
Post-secondary, ≥ 3 years	533710 (33.77)	6585 (29.21)	527125 (33.83)
Postgraduate	19248 (1.22)	178 (0.79)	19070 (1.22)
Nationality (Swedish)	1281142 (81.05)	20361 (90.32)	1260781 (80.92)
Criminal convictions (any)	173631 (10.98)	3973 (17.62)	169658 (10.89)
Severe psychiatric problem[c]	16736 (1.06)	1734 (7.69)	15002 (0.96)
Suicide attempt (definite or uncertain)	66655 (4.22)	3251 (14.42)	63404 (4.07)
Paternal covariates			
Age at birth			
< 20 years	7789 (0.49)	134 (0.59)	7655 (0.49)
20 to 24 years	100339 (6.35)	1543 (6.84)	98796 (6.34)
25 to 29 years	364992 (23.09)	4815 (21.36)	360177 (23.12)
30 to 34 years	547663 (34.65)	7118 (31.57)	540545 (34.69)
35 to 39 years	355300 (22.48)	5380 (23.86)	349920 (22.46)
≥ 40 years	204546 (12.94)	3554 (15.76)	200992 (12.90)
Education			
Primary and lower secondary, < 9 years	29369 (1.86)	257 (1.14)	29112 (1.87)

Primary and lower secondary, 9 years	153577 (9.72)	2672 (11.85)	150905 (9.69)
Upper secondary, 1-2 years	403919 (25.55)	5647 (25.05)	398272 (25.56)
Upper secondary, 3 years	381746 (24.15)	6271 (27.82)	375475 (24.10)
Post-secondary, < 3 years	233560 (14.78)	2930 (13.00)	230630 (14.80)
Post-secondary, ≥ 3 years	348397 (22.04)	4404 (19.54)	343993 (22.08)
Postgraduate	30061 (1.90)	363 (1.61)	29698 (1.91)
Nationality (Swedish)	1273973 (80.60)	19699 (87.38)	1254274 (80.50)
Criminal convictions (any)	582002 (36.82)	9313 (41.31)	572689 (36.76)
Severe psychiatric problem[c]	10373 (0.66)	321 (1.42)	10052 (0.65)
Suicide attempt (definite or uncertain)	64879 (4.10)	1364 (6.05)	63515 (4.08)

All percentages are based on the number of offspring. [a]Age 15 Kaplan Meier estimates. [b]Year of birth is presented in bins in Table II.1 but was not binned when used as a covariate in models. [c]Severe psychiatric problem was defined as an inpatient or outpatient diagnosis of schizophrenia, bipolar disorder, or other non-drug induced psychosis.

Table II.2. Baseline, adjusted, and sibling comparison associations between maternal self-reported first-trimester use and birth and neurodevelopmental outcomes

	Baseline Model		Adjusted Model		Sibling Comparison	
Any antidepressant						
	OR	**95% CI**	**OR**	**95% CI**	**OR.**	**95% CI**
Preterm birth	1.47	1.40-1.55	1.35	1.28-1.42	1.34	1.18-1.52
Small for gestational age	1.15	1.06-1.25	1.12	1.03-1.22	1.01	0.81-1.25
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Autism spectrum disorder	2.02	1.80-2.26	1.64	1.46-1.83	0.83	0.62-1.13
Attention-deficit/hyperactivity disorder	2.21	2.04-2.39	1.58	1.46-1.71	0.99	0.79-1.25
SSRIs						
	OR	**95% CI**	**OR**	**95% CI**	**OR.**	**95% CI**
Preterm birth	1.38	1.30-1.46	1.27	1.20-1.35	1.33	1.16-1.53
Small for gestational age	1.11	1.01-1.21	1.09	0.99-1.20	0.88	0.70-1.12
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Autism spectrum disorder	2.04	1.80-2.32	1.66	1.46-1.89	0.81	0.58-1.14
Attention-deficit/hyperactivity disorder	2.25	2.06-2.46	1.60	1.47-1.75	0.94	0.73-1.22

OR=odds ratio. HR=hazard ratio. CI=confidence interval. Baseline and adjusted models were fit in a sample of 1,580,629 offspring. See SII.1 Appendix for information about offspring who could be informative in sibling comparisons. Baseline models controlled for parity and year of birth. Adjusted models controlled for parity and year of birth and maternal and paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts. Sibling comparisons controlled for parity and year of birth, paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts, and maternal age at childbearing.

Table II.3. Adjusted associations between maternal antidepressant dispensations before pregnancy and during the first trimester of pregnancy and birth and neurodevelopmental outcomes

	Before pregnancy		1st trimester	
Any antidepressant				
	OR	**95% CI**	**OR**	**95% CI**
Preterm birth	1.17	1.07-1.28	1.40	1.33-1.47
Small for gestational age	1.07	0.93-1.24	1.12	1.03-1.21
	HR	**95% CI**	**HR**	**95% CI**
Autism spectrum disorder	1.40	1.02-1.93	1.75	1.49-2.07
Attention-deficit/hyperactivity disorder	2.09	1.53-2.86	1.85	1.55-2.20
SSRIs				
	OR	**95% CI**	**OR**	**95% CI**
Preterm birth	1.13	1.02-1.25	1.37	1.30-1.45
Small for gestational age	1.09	0.94-1.28	1.13	1.03-1.23
	HR	**95% CI**	**HR**	**95% CI**
Autism spectrum disorder	1.49	1.06-2.10	1.72	1.43-2.06
Attention-deficit/hyperactivity disorder	1.93	1.35-2.74	1.81	1.50-2.19

OR=odds ratio. HR=hazard ratio. CI=confidence interval. All models were fit in a sample of 708,450 offspring. Models controlled parity and year of birth and maternal and paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts.

Table II.4. Baseline associations between paternal first-trimester antidepressant dispensations and birth and neurodevelopmental outcomes

	Any Antidepressant		SSRIs	
	OR	**95% CI**	**OR**	**95% CI**
Preterm birth	1.13	1.05-1.20	1.13	1.05-1.22
Small for gestational age	1.06	0.96-1.17	1.00	0.89-1.13
	HR	**95% CI**	**HR**	**95% CI**
Autism spectrum disorder	1.31	1.05-1.62	1.27	0.98-1.65
Attention-deficit/hyperactivity disorder	1.73	1.38-2.17	1.71	1.31-2.23

OR=odds ratio. HR=hazard ratio. CI=confidence interval. All models were fit in a sample of 708,450 offspring. Models controlled for parity and year of birth. Analyses compared offspring of fathers with first trimester antidepressant dispensations to offspring of fathers who were not dispensed antidepressants before pregnancy, during the second and third trimester of pregnancy, and after pregnancy (sFigure II.1 shows dispensation windows).

Refernces

1. Bakker MK, Kolling P, van den Berg PB, de Walle HEK, van den Berg L. Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. *British journal of clinical pharmacology.* 2008;65(4):600-606.
2. Huang H, Coleman S, Bridge JA, Yonkers K, Katon W. A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight. *Gen Hosp Psychiatry.* 2014;36(1):13-18.
3. Boukhris T, Sheehy O, Mottron L, Berard A. Antidepressant Use During Pregnancy and the Risk of Autism Spectrum Disorder in Children. *JAMA Pediatr.* 2016;170(2):117-124.
4. Croen LA, Grether JK, Yoshida CK, Odouli R, Hendrick V. Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch Gen Psychiatry.* 2011;68(11):1104-1112.
5. El Marroun H, White TJ, van der Knaap NJ, et al. Prenatal exposure to selective serotonin reuptake inhibitors and social responsiveness symptoms of autism: population-based study of young children. *Br J Psychiatry.* 2014;205(2):95-102.
6. Harrington RA, Lee LC, Crum RM, Zimmerman AW, Hertz-Picciotto I. Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. *Pediatrics.* 2014;133(5):e1241-1248.
7. Clements CC, Castro VM, Blumenthal SR, et al. Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system. *Mol Psychiatry.* 2015;20(6):727-734.

8. Whitaker-Azmitia PM. Serotonin and brain development: role in human developmental diseases. *Brain Res Bull.* 2001;56(5):479-485.

9. Jarde A, Morais M, Kingston D, et al. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: A systematic review and meta-analysis. *JAMA Psychiatry.* 2016;73(8):826-837.

10. Talge NM, Neal C, Glover V. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *Journal of Child Psychology and Psychiatry.* 2007;48(3-4):245-261.

11. Lichtenstein P, Carlstrom E, Rastam M, Gillberg C, Anckarsater H. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am J Psychiatry.* 2010;167(11):1357-1363.

12. Scherff A, Taylor M, Eley TC, Happe F, Charman T, Ronald A. What causes internalising traits and autistic traits to co-occur in adolescence? A community-based twin study. *J Abnorm Child Psychol.* 2014;42(4):601-610.

13. Cole J, Ball HA, Martin NC, Scourfield J, McGuffin P. Genetic overlap between measures of hyperactivity/inattention and mood in children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 2009;48(11):1094-1101.

14. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *General Hospital Psychiatry.* 2009;31(5):403-413.

15. Academy of Medical Sciences Working Group. *Identifying the environmental causes of disease: How should we decide what to believe and when to take action?* London: Academy of Medical Sciences; 2007.

16. Larsson H, Ryden E, Boman M, Langstrom N, Lichtenstein P, Landen M. Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. *British Journal of Psychiatry.* 2013;203(2):103-106.

17. Lundström S, Reichenberg A, Anckarsäter H, Lichtenstein P, Gillberg C. Autism phenotype versus registered diagnosis in Swedish children: prevalence trends over 10 years in general population samples. *The BMJ.* 2015;350:h1961.

18. D'Onofrio BM, Class QA, Rickert ME, Larsson H, Langstrom N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. *JAMA Psychiatry.* 2013;70(11):1231-1240.

19. D'Onofrio BM, Rickert ME, Frans E, et al. Paternal age at childbearing and offspring psychiatric and academic morbidity. *JAMA Psychiatry.* 2014;71(4):432-438.

20. Bramson LM, Rickert ME, Class QA, et al. The association between childhood relocations and subsequent risk of suicide attempt, psychiatric problems, and low academic achievement. *Psychological Medicine.* 2016;46(5):969-979.

21. Kendler KS, Lönn SL, Morris NA, Sundquist J, Långström N, Sundquist K. A Swedish national adoption study of criminality. *Psychological Medicine.* 2014;44(9):1913-1925.

22. D'Onofrio BM, Class QA, Rickert ME, et al. Translational Epidemiologic Approaches to Understanding the Consequences of Early-Life Exposures. *Behav Genet.* 2016;46(3):315-328.

23. Allison PD. *Fixed effects regression models.* Washington DC: Sage; 2009.

24. Huybrechts KF, Sanghani RS, Avorn J, Urato AC. Preterm birth and antidepressant medication use during pregnancy: a systematic review and meta-analysis. *PLoS ONE.* 2014;9(3):e92778.

25. Viktorin A, Lichtenstein P, Lundholm C, et al. Selective serotonin re-uptake inhibitor use during pregnancy: association with offspring birth size and gestational age. *International Journal of Epidemiology.* 2016;45(1):170-177.

26. Sorensen MJ, Gronborg TK, Christensen J, et al. Antidepressant exposure in pregnancy and risk of autism spectrum disorders. *Clin Epidemiol.* 2013;5:449-459.

27. Palmsten K, Hernández-Díaz S. Can non-randomized studies on the safety of antidepressants during pregnancy convincingly beat confounding, chance, and prior beliefs? *Epidemiology (Cambridge, Mass).* 2012;23(5):686-688.

28. Frisell T, Oberg AS, Kuja-Halkola R, Sjolander A. Sibling comparison designs: Bias from non-shared confounders and measurement error. *Epidemiology.* 2012;23:713-720.

29. Suri R, Altshuler L, Hellemann G, Burt VK, Aquino A, Mintz J. Effects of antenatal depression and antidepressant treatment on gestational age at birth and risk of preterm birth. *Am J Psychiatry.* 2007;164(8):1206-1213.

30. Boukhris T, Bérard A. Selective Serotonin Reuptake Inhibitor Use during Pregnancy and the Risk of Autism Spectrum Disorders: A Review. *J Pediatr Genet.* 2015;04(02):084-093.

31. Kaplan Y, Keskin-Arslan E, Acar S. Prenatal antidepressant use and risk of autism spectrum disorders in children. *JAMA Pediatrics.* 2016;170(7):712.

32. Fombonne E. Prenatal antidepressant use and risk of autism spectrum disorders in the children. *JAMA Pediatrics.* 2016;170(7):711-712.

33. Gauderman WJ, Witte JS, Thomas DC. Family-based association studies. *J Natl Cancer Inst Monogr.* 1999(26):31-37.

SII.1 Appendix: Descriptive Statistics Based on Maternal Self-reported Antidepressant Use

In the main paper, we presented the distribution of covariates and outcomes stratified by maternal self-reported use of any antidepressant (Table II.1). We have also provided the distribution of outcomes and covariates stratified by maternal self-reported use of any antidepressant in a subsample of differentially exposed siblings (sTable II.1), as well as the distribution of outcomes and covariates stratified by maternal self-reported use of SSRIs specifically in all offspring in the sample and in a subsample of differentially exposed siblings (sTables II.2 and II.3, respectively). Because families in which all siblings are concordant on the outcomes cannot contribute to sibling comparison analyses, we have also provided information about subsamples of offspring from families with outcome-discordant siblings (sTable II.4).

sTable II.1. Descriptive statistics stratified by maternal self-reported first-trimester use of any antidepressant in a subsample of differentially exposed siblings

	Exposed offspring (n=10,975)	**Unexposed offspring** (n=13,994)
	No. (%)	**No. (%)**
Offspring outcomes		
Preterm birth	685 (6.24)	710 (5.07)
Small for gestational age	205 (1.87)	277 (1.98)
Autism spectrum disorder[a]	136 (5.52)	274 (4.55)
Attention-deficit/hyperactivity disorder[a]	280 (12.38)	699 (12.73)
Pregnancy covariates		
First born	2942 (26.81)	5803 (41.47)
Second born	4279 (38.99)	5346 (38.20)
Third born	2506 (22.83)	1803 (12.88)
Fourth born or higher	1248 (11.37)	1042 (7.45)
Born 1996 to 1999[b]	534 (4.87)	2648 (18.92)
Born 2000 to 2003[b]	1592 (14.51)	3653 (26.10)
Born 2004 to 2007[b]	3658 (33.33)	3882 (27.74)
Born 2008 to 2012[b]	5191 (47.30)	3811 (27.23)
Maternal covariates		
Age at birth		
< 20 years	111 (1.01)	509 (3.64)
20 to 24 years	1203 (10.96)	3158 (22.57)
25 to 29 years	3061 (27.89)	4720 (33.73)
30 to 34 years	3853 (35.11)	3800 (27.15)
35 to 39 years	2290 (20.87)	1543 (11.03)
≥ 40 years	457 (4.16)	264 (1.89)
Education		
Primary and lower secondary, < 9 years	99 (0.90)	141 (1.01)
Primary and lower secondary, 9 years	1375 (12.53)	1892 (13.52)
Upper secondary, 1-2 years	1951 (17.78)	2607 (18.63)
Upper secondary, 3 years	3022 (27.54)	3850 (27.51)
Post-secondary, < 3 years	1363 (12.42)	1670 (11.93)
Post-secondary, ≥ 3 years	3077 (28.04)	3737 (26.70)
Postgraduate	88 (0.80)	97 (0.69)
Nationality (Swedish)	9856 (89.80)	12469 (89.10)
Criminal convictions (any)	2007 (18.29)	2722 (19.45)
Severe psychiatric problem[c]	812 (7.40)	991 (7.08)
Suicide attempt (definite or uncertain)	1552 (14.14)	2018 (14.42)
Paternal covariates		
Age at birth		
< 20 years	50 (0.46)	191 (1.36)
20 to 24 years	706 (6.43)	1760 (12.58)
25 to 29 years	2358 (21.49)	4192 (29.96)
30 to 34 years	3571 (32.54)	4241 (30.31)
35 to 39 years	2666 (24.29)	2374 (16.96)
≥ 40 years	1624 (14.80)	1236 (8.83)
Education		
Primary and lower secondary, < 9 years	137 (1.25)	180 (1.29)

	Exposed offspring (n=10,975)	**Unexposed offspring** (n=13,994)
	No. (%)	**No. (%)**
Primary and lower secondary, 9 years	1290 (11.75)	1769 (12.64)
Upper secondary, 1-2 years	2810 (25.60)	3748 (26.78)
Upper secondary, 3 years	3076 (28.03)	3872 (27.67)
Post-secondary, < 3 years	1422 (12.96)	1788 (12.78)
Post-secondary, ≥ 3 years	2061 (18.78)	2420 (17.29)
Postgraduate	179 (1.63)	217 (1.55)
Nationality (Swedish)	9533 (86.86)	12023 (85.92)
Criminal convictions (any)	4603 (41.94)	6206 (44.35)
Severe psychiatric problem[c]	152 (1.38)	175 (1.25)
Suicide attempt (definite or uncertain)	621 (5.66)	802 (5.73)

All percentages are based on the number of offspring. [a]Age 15 Kaplan Meier estimates. [b]Year of birth is presented in bins in sTable II.1 but was not binned when used as a covariate in models. [c]Severe psychiatric problem was defined as an inpatient or outpatient diagnosis of schizophrenia, bipolar disorder, or other non-drug induced psychosis.

sTable II.2. Descriptive statistics stratified by maternal self-reported first-trimester SSRI use

	Exposed offspring (n=18,470)	**Unexposed offspring** (n=1,562,159)
	No. (%)	**No. (%)**
Offspring outcomes		
Preterm birth	1214 (6.57)	74847 (4.79)
Small for gestational age	453 (2.45)	34275 (2.19)
Autism spectrum disorder[a]	236 (5.21)	14381 (2.14)
Attention-deficit/hyperactivity disorder[a]	476 (13.29)	32448 (5.47)
Pregnancy covariates		
First born	8658 (46.88)	684412 (43.81)
Second born	5717 (30.95)	579902 (37.12)
Third born	2777 (15.04)	210605 (13.48)
Fourth born or higher	1318 (7.14)	87240 (5.58)
Born 1996 to 1999[b]	1063 (5.76)	332728 (21.30)
Born 2000 to 2003[b]	2340 (12.67)	346803 (22.20)
Born 2004 to 2007[b]	5230 (28.32)	381281 (24.41)
Born 2008 to 2012[b]	9837 (53.26)	501347 (32.09)
Maternal covariates		
Age at birth		
< 20 years	290 (1.57)	25347 (1.62)
20 to 24 years	2224 (12.04)	208328 (13.34)
25 to 29 years	5123 (27.74)	489927 (31.36)
30 to 34 years	6146 (33.28)	538600 (34.48)
35 to 39 years	3794 (20.54)	250977 (16.07)
≥ 40 years	893 (4.83)	48980 (3.14)
Education		
Primary and lower secondary, < 9 years	133 (0.72)	33515 (2.15)
Primary and lower secondary, 9 years	2115 (11.45)	105838 (6.78)
Upper secondary, 1-2 years	3009 (16.29)	243406 (15.58)
Upper secondary, 3 years	5043 (27.30)	409906 (26.24)
Post-secondary, < 3 years	2450 (13.26)	222256 (14.23)
Post-secondary, ≥ 3 years	5588 (30.25)	528122 (33.81)
Postgraduate	132 (0.71)	19116 (1.22)
Nationality (Swedish)	16719 (90.52)	1264423 (80.94)
Criminal convictions (any)	3158 (17.10)	170473 (10.91)
Severe psychiatric problem[c]	1350 (7.31)	15386 (0.98)
Suicide attempt (definite or uncertain)	2530 (13.70)	64125 (4.10)
Paternal covariates		
Age at birth		
< 20 years	116 (0.63)	7673 (0.49)
20 to 24 years	1287 (6.97)	99052 (6.34)
25 to 29 years	3973 (21.51)	361019 (23.11)
30 to 34 years	5890 (31.89)	541773 (34.68)
35 to 39 years	4371 (23.67)	350929 (22.46)
≥ 40 years	2833 (15.34)	201713 (12.91)
Education		
Primary and lower secondary, < 9 years	194 (1.05)	29175 (1.87)
	Exposed offspring (n=18,470)	**Unexposed offspring** (n=1,562,159)

	No. (%)	No. (%)
Primary and lower secondary, 9 years	2141 (11.59)	151436 (9.69)
Upper secondary, 1-2 years	4460 (24.15)	399459 (25.57)
Upper secondary, 3 years	5261 (28.48)	376485 (24.10)
Post-secondary, < 3 years	2408 (13.04)	231152 (14.80)
Post-secondary, ≥ 3 years	3697 (20.02)	344700 (22.07)
Postgraduate	309 (1.67)	29752 (1.90)
Nationality (Swedish)	16195 (87.68)	1257778 (80.52)
Criminal convictions (any)	7538 (40.81)	574464 (36.77)
Severe psychiatric problem[c]	247 (1.34)	10126 (0.65)
Suicide attempt (definite or uncertain)	1082 (5.86)	63797 (4.08)

All percentages are based on the number of offspring. [a]Age 15 Kaplan Meier estimates. [b]Year of birth is presented in bins in sTable II.2 but was not binned when used as a covariate in models. [c]Severe psychiatric problem was defined as an inpatient or outpatient diagnosis of schizophrenia, bipolar disorder, or other non-drug induced psychosis.

sTable II.3. Descriptive statistics stratified by maternal self-reported first-trimester use of SSRIs in a subsample of differentially exposed siblings

	Exposed offspring (n=9,063)	**Unexposed offspring** (n=15,906)
	No. (%)	**No. (%)**
Offspring outcomes		
Preterm birth	544 (6.00)	851 (5.35)
Small for gestational age	162 (1.79)	320 (2.01)
Autism spectrum disorder[a]	108 (5.59)	229 (4.64)
Attention-deficit/hyperactivity disorder[a]	229 (13.61)	585 (13.00)
Pregnancy covariates		
First born	2377 (26.23)	6368 (40.04)
Second born	3639 (40.15)	5986 (37.63)
Third born	2072 (22.86)	2237 (14.06)
Fourth born or higher	975 (10.76)	1315 (8.27)
Born 1996 to 1999[b]	369 (4.07)	2813 (17.69)
Born 2000 to 2003[b]	1256 (13.86)	3989 (25.08)
Born 2004 to 2007[b]	3027 (33.40)	4513 (28.37)
Born 2008 to 2012[b]	4411 (48.67)	4591 (28.86)
Maternal covariates		
Age at birth		
< 20 years	96 (1.06)	524 (3.29)
20 to 24 years	1003 (11.07)	3358 (21.11)
25 to 29 years	2554 (28.18)	5227 (32.86)
30 to 34 years	3146 (34.71)	4507 (28.34)
35 to 39 years	1888 (20.83)	1945 (12.23)
≥ 40 years	376 (4.15)	345 (2.17)
Education		
Primary and lower secondary, < 9 years	83 (0.92)	157 (0.99)
Primary and lower secondary, 9 years	1075 (11.86)	2192 (13.78)
Upper secondary, 1-2 years	1555 (17.16)	3003 (18.88)
Upper secondary, 3 years	2548 (28.11)	4324 (27.18)
Post-secondary, < 3 years	1118 (12.34)	1915 (12.04)
Post-secondary, ≥ 3 years	2614 (28.84)	4200 (26.41)
Postgraduate	70 (0.77)	115 (0.72)
Nationality (Swedish)	8157 (90.00)	14168 (89.07)
Criminal convictions (any)	1607 (17.73)	3122 (19.63)
Severe psychiatric problem[c]	630 (6.95)	1173 (7.37)
Suicide attempt (definite or uncertain)	1203 (13.27)	2367 (14.88)
Paternal covariates		
Age at birth		
< 20 years	42 (0.46)	199 (1.25)
20 to 24 years	580 (6.40)	1886 (11.86)
25 to 29 years	1933 (21.33)	4617 (29.03)
30 to 34 years	2989 (32.98)	4823 (30.32)
35 to 39 years	2189 (24.15)	2851 (17.92)
≥ 40 years	1330 (14.68)	1530 (9.62)
Education		
Primary and lower secondary, < 9 years	108 (1.19)	209 (1.31)

	Exposed offspring (n=9,063)	**Unexposed offspring** (n=15,906)
	No. (%)	**No. (%)**
Primary and lower secondary, 9 years	1054 (11.63)	2005 (12.61)
Upper secondary, 1-2 years	2283 (25.19)	4275 (26.88)
Upper secondary, 3 years	2557 (28.21)	4391 (27.61)
Post-secondary, < 3 years	1180 (13.02)	2030 (12.76)
Post-secondary, ≥ 3 years	1727 (19.06)	2754 (17.31)
Postgraduate	154 (1.70)	242 (1.52)
Nationality (Swedish)	7898 (87.15)	13658 (85.87)
Criminal convictions (any)	3771 (41.61)	7038 (44.25)
Severe psychiatric problem[c]	122 (1.35)	205 (1.29)
Suicide attempt (definite or uncertain)	499 (5.51)	924 (5.81)

All percentages are based on the number of offspring. [a]Age 15 Kaplan Meier estimates. [b]Year of birth is presented in bins in sTable II.3 but was not binned when used as a covariate in models. [c]Severe psychiatric problem was defined as an inpatient or outpatient diagnosis of schizophrenia, bipolar disorder, or other non-drug induced psychosis.

sTable II.4. Information on families with outcome discordant siblings in the cohort born 1996 to 2012

	Number of distinct outcome discordant siblings	Number of distinct mothers with outcome discordant offspring	Number of siblings with outcomes
Preterm birth	96866	40416	42557
Small for gestational age	45155	18926	19581
Autism spectrum disorder	24969	10105	10371
Attention-deficit/hyperactivity disorder	55526	22301	23522

SII.2 Appendix: Descriptive Statistics and Analyses Based on Antidepressant Dispensation Records

Exposure status was based on dispensation data for the timing of exposure comparisons and paternal comparisons. Dispensation windows used in main analyses were: (1) only before pregnancy, (2) during the first trimester of pregnancy, (3) only during the second and/or third trimester, and (4) only after pregnancy (see sFigure II.1 for a diagram of the dispensation windows). We have presented the distribution of outcomes and covariates stratified by maternal dispensation windows for any antidepressants and for SSRIs specifically (sTables 5 and 6, respectively). In addition, we have presented the distribution of outcomes and covariates for offspring of fathers with first-trimester dispensations and offspring of fathers without dispensations before, during, or after pregnancy (see sTable II.7 for any antidepressant dispensations and sTable II.8 for SSRI dispensations).

Timing of exposure analyses compared associations with dispensations before pregnancy to associations with first-trimester dispensations. We evaluated whether these associations differed statistically using Wald χ^2 tests. We also compared the fit of two models using the Akaike information criterion (AIC). The first model included four parameters that compared the following groups to offspring unexposed to any antidepressants: (1) dispensations only before pregnancy, (2) dispensations for the first trimester of pregnancy, (3) dispensations only for the second and/or third trimester of pregnancy, and (4) dispensations only after pregnancy. The second model constrained the first two parameters to be equal so that the model included the following three parameters: (1) dispensations before and/or during the first trimester of pregnancy, (2) dispensations for the second and/or third trimester of pregnancy, and (3) dispensations after pregnancy. Thus, the four-parameter model included separate parameters for

dispensations before pregnancy and first-trimester dispensations, whereas the three-parameter model included one parameter for dispensations before pregnancy and first-trimester dispensations. If associations with dispensations before pregnancy differed from associations with dispensations during the first trimester of pregnancy, the model that included separate parameters for those two time periods would fit better.

For preterm birth, the association between dispensations before pregnancy and preterm birth was significantly smaller than the association between first-trimester dispensations and preterm birth (p=0.0007 for any antidepressant, p=0.001 for SSRIs specifically), and the four-parameter model fit better than the three-parameter model. However, for small for gestational age, autism spectrum disorder, and attention-deficit/hyperactivity disorder the associations with dispensations before pregnancy did not significantly differ from associations with first-trimester dispensations (small for gestational age: p=0.64 for any antidepressant, p=0.74 for SSRIs specifically; autism spectrum disorder: p=0.21 for any antidepressant, p=0.46 for SSRIs specifically; attention-deficit/hyperactivity disorder: p=0.49 for any antidepressant, p=0.76 for SSRIs specifically). The three-parameter model also fit better than the four-parameter model for these outcomes. The four-parameter model estimates and the model fit for both models are presented in sTable II.9.

sTable II.5. Descriptive statistics stratified by maternal dispensation windows for any antidepressants

	Before pregnancy dispensations only (n=8203 [1.16%])	**1st-trimester dispensations** (n=26477 [3.74%])	**2nd and/or 3rd trimester dispensations only** (n=746 [0.11%])	**After pregnancy dispensations only** (n=6574 [0.93%])	**No dispensations before, during, or after pregnancy** (n=666450)
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Offspring outcomes					
Preterm birth	484 (5.90)	1842 (6.96)	42 (5.63)	419 (6.37)	30945 (4.64)
Small for gestational age	205 (2.50)	660 (2.49)	20 (2.68)	148 (2.25)	14348 (2.15)
Autism spectrum disorder[a]	35 (0.96)	143 (1.14)	6 (2.00)	29 (0.90)	2044 (0.59)
Attention-deficit/hyperactivity disorder[a]	27 (1.03)	80 (0.83)	0 (0.00)	24 (0.88)	931 (0.34)
Pregnancy covariates					
First born	4097 (49.95)	12244 (46.24)	281 (37.67)	2666 (40.55)	296400 (44.47)
Second born	2298 (28.01)	8224 (31.06)	261 (34.99)	2586 (39.34)	250549 (37.59)
Third born	1219 (14.86)	4031 (15.22)	130 (17.43)	898 (13.66)	85821 912.88)
Fourth born or higher	589 (7.18)	1978 (7.47)	74 (9.92)	424 (6.45)	33680 (5.05)
Born 2006 to 2009[b]	4316 (52.61)	13570 (51.25)	364 (48.79)	3514 (53.45)	377773 (56.68)
Born 2010 to 2012[b]	3887 (47.39)	12907 (48.75)	382 (51.21)	3060 (46.55)	288677 (43.32)
Maternal covariates					
Age at birth					
< 20 years	152 (1.85)	439 (1.66)	20 (2.68)	172 (2.62)	9470 (1.42)
20 to 24 years	1244 (15.17)	3345 (12.63)	134 (17.96)	1080 (16.43)	84356 (12.66)
25 to 29 years	2257 (27.51)	7030 (26.55)	211 (28.28)	1871 (28.46)	193442 (29.03)
30 to 34 years	2660 (32.43)	8710 (32.90)	203 (27.21)	2080 (31.64)	234498 (35.19)
35 to 39 years	1522 (18.55)	5549 (20.96)	133 (17.83)	1088 (16.55)	120041 (18.01)
≥ 40 years	368 (4.49)	1404 (5.30)	45 (6.03)	283 (4.30)	24643 (3.70)
Education					
Primary and lower secondary, < 9 years	152 (1.85)	346 (1.31)	28 (3.75)	108 (1.64)	17093 (2.56)
Primary and lower secondary, 9 years	1077 (13.13)	3482 (13.15)	138 (18.58)	941 (14.31)	44637 (6.70)
Upper secondary, 1-2 years	1103 (13.45)	3513 (13.27)	97 (13.00)	820 (12.47)	61107 (9.17)
Upper secondary, 3 years	2363 (28.81)	7534 (28.45)	186 (24.93)	1922 (29.24)	189191 (28.39)
Post-secondary, < 3 years	1030 (12.56)	3358 (12.68)	104 (13.94)	789 (12.00)	84692 (12.71)
Post-secondary, ≥ 3 years	2408 (29.36)	8045 (30.38)	189 (25.34)	1956 (29.75)	261200 (39.19)
Postgraduate	70 (0.85)	199 (0.75)	4 (0.54)	38 (0.58)	8530 (1.28)
	Before pregnancy	**1st-trimester dispensations**	**2nd and/or 3rd trimester**	**After pregnancy**	**No dispensations before, during,**

	dispensations only (n=8203 [1.16%])	(n=26477 [3.74%])	**dispensations only** (n=746 [0.11%])	**dispensations only** (n=6574 [0.93%])	**or after pregnancy** (n=66450)
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Nationality (Swedish)	6839 (83.37)	23220 (87.70)	543 (72.79)	5481 (83.37)	523334 (78.53)
Criminal convictions (any)	1417 (17.27)	4676 (17.66)	158 (21.18)	1058 (16.09)	62678 (9.40)
Severe psychiatric problem[c]	336 (4.10)	1736 (6.56)	37 (4.96)	370 (5.63)	3604 (0.54)
Suicide attempt (definite or uncertain)	1003 (12.23)	3685 (13.92)	101 (13.54)	676 (10.28)	23861 (3.58)
Paternal covariates					
Age at birth					
< 20 years	55 (0.67)	185 (0.70)	11 (1.47)	50 (0.76)	3033 (0.46)
20 to 24 years	708 (8.63)	2006 (7.58)	73 (9.79)	599 (9.11)	39498 (5.93)
25 to 29 years	1801 (21.96)	5543 (20.94)	165 (22.12)	1461 (22.22)	139335 (20.91)
30 to 34 years	2464 (30.04)	8096 (30.58)	200 (26.81)	2101 (31.96)	226642 (34.01)
35 to 39 years	1897 (23.13)	6260 (23.64)	176 (23.59)	1472 (22.39)	161388 (24.22)
≥ 40 years	1278 (15.58)	4387 (16.57)	121 (16.22)	891 (13.55)	96554 (14.49)
Education					
Primary and lower secondary, < 9 years	165 (2.01)	398 (1.50)	21 (2.82)	131 (1.99)	14251 (2.14)
Primary and lower secondary, 9 years	1027 (12.52)	3200 (12.09)	96 (12.87)	799 (12.15)	59882 (8.99)
Upper secondary, 1-2 years	1569 (19.13)	5345 (20.19)	150 (20.11)	1234 (18.77)	111799 (16.78)
Upper secondary, 3 years	2569 (31.32)	8243 (31.13)	224 (30.03)	2189 (33.30)	200790 (30.13)
Post-secondary, < 3 years	1052 (12.82)	3394 (12.82)	101 (13.54)	827 (12.58)	94032 (14.11)
Post-secondary, ≥ 3 years	1740 (21.21)	5536 (20.91)	143 (19.17)	1315 (20.00)	173513 (26.04)
Postgraduate	81 (0.99)	361 (1.36)	11 (1.47)	79 (1.20)	12183 (1.83)
Nationality (Swedish)	6704 (81.73)	22443 (84.76)	535 (71.72)	5415 (82.37)	522698 (78.43)
Criminal convictions (any)	3263 (39.78)	10434 (39.41)	309 (41.42)	2516 (38.27)	213431 (32.03)
Severe psychiatric problem[c]	78 (0.95)	351 (1.33)	8 (1.07)	88 (1.34)	3177 (0.48)
Suicide attempt (definite or uncertain)	488 (5.95)	1560 (5.89)	46 (6.17)	343 (5.22)	25464 (3.82)

All percentages are based on the number of offspring. [a]Age 6 Kaplan Meier estimates. [b]Year of birth is presented in bins in sTable II.5 but was not binned when used as a covariate in models. [c]Severe psychiatric problem was defined as an inpatient or outpatient diagnosis of schizophrenia, bipolar disorder, or other non-drug induced psychosis.

sTable II.6. Descriptive statistics stratified by maternal dispensation windows for SSRIs

	Before pregnancy dispensations (n=6674 [0.94%])	**1st-trimester dispensations** (n=22125 [3.12%])	**2nd/3rd trimester dispensations** (n=775 [0.11%])	**After pregnancy dispensations** (n=6007 [0.85%])	**No dispensations before, during, or after pregnancy** (n=672869)
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Offspring outcomes					
Preterm birth	381 (5.71)	1512 (6.83)	41 (5.29)	378 (6.29)	31420 (4.67)
Small for gestational age	167 (2.50)	550 (2.49)	21 (2.71)	130 (2.16)	14513 (2.16)
Autism spectrum disorder[a]	30 (1.05)	115 (1.10)	6 (1.89)	31 (1.04)	2075 (0.59)
Attention-deficit/hyperactivity disorder[a]	21 (0.98)	64 (0.79)	1 (0.38)	24 (0.96)	952 (0.35)
Pregnancy covariates					
First born	3294 (49.36)	10220 (46.19)	293 (37.81)	2471 (41.14)	299410 (44.50)
Second born	1928 (28.89)	7022 (31.74)	274 (35.25)	2370 (39.45)	252324 (37.50)
Third born	997 (14.94)	3325 (15.03)	130 (16.77)	803 (13.37)	86844 (12.91)
Fourth born or higher	455 (6.82)	1558 (7.04)	78 (10.06)	363 (6.04)	34291 (5.10)
Born 2006 to 2009[b]	3550 (53.19)	11212 (50.68)	374 (48.26)	3192 (53.14)	381209 (56.65)
Born 2010 to 2012[b]	3124 (46.81)	10913 (49.32)	401 (51.74)	2815 (46.86)	291660 (43.35)
Maternal covariates					
Age at birth					
< 20 years	141 (2.11)	387 (1.75)	20 (2.58)	153 (2.55)	9552 (1.42)
20 to 24 years	1021 (15.30)	2826 (12.77)	140 (18.06)	1000 (16.65)	85172 (12.66)
25 to 29 years	1855 (27.79)	5926 (26.78)	218 (28.13)	1694 (28.20)	195118 (29.00)
30 to 34 years	2158 (32.33)	7269 (32.85)	216 (27.87)	1889 (31.45)	236619 (35.17)
35 to 39 years	1214 (18.19)	4580 (20.70)	137 (17.68)	1019 (16.96)	121383 (18.04)
≥ 40 years	285 (4.27)	1137 (5.14)	44 (5.68)	252 (4.20)	25025 (3.72)
Education					
Primary and lower secondary, < 9 years	108 (1.62)	254 (1.15)	29 (3.74)	90 (1.50)	17246 (2.56)
Primary and lower secondary, 9 years	880 (13.19)	2795 (12.63)	149 (19.23)	831 (13.83)	45620 (6.78)
Upper secondary, 1-2 years	857 (12.84)	2802 (12.66)	104 (13.42)	740 (12.32)	62137 (9.23)
Upper secondary, 3 years	1901 (28.48)	6303 (28.49)	194 (25.03)	1756 (29.23)	191042 (28.39)
Post-secondary, < 3 years	861 (12.90)	2831 (12.80)	109 (14.06)	730 (12.15)	85442 (12.70)
Post-secondary, ≥ 3 years	2012 (30.15)	6973 (31.52)	185 (23.87)	1824 (30.36)	262804 (39.06)
Postgraduate	55 (0.82)	167 (0.75)	5 (0.65)	36 (0.60)	8578 (1.27)
	Before pregnancy dispensations (n=6674 [0.94%])	**1st-trimester dispensations** (n=22125 [3.12%])	**2nd/3rd trimester dispensations** (n=775 [0.11%])	**After pregnancy dispensations** (n=6007 [0.85%])	**No dispensations before, during, or after pregnancy**

					(n=672869)
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Nationality (Swedish)	5616 (84.15)	19486 (88.07)	570 (73.55)	5036 (83.84)	528709 (78.58)
Criminal convictions (any)	1160 (17.38)	3750 (16.95)	165 (21.29)	974 (16.21)	63938 (9.50)
Severe psychiatric problem[c]	278 (4.17)	1418 (6.41)	49 (6.32)	358 (5.96)	3980 (0.59)
Suicide attempt (definite or uncertain)	817 (12.24)	2927 (13.23)	112 (14.45)	625 (10.40)	24845 (3.69)
Paternal covariates					
Age at birth					
< 20 years	46 (0.69)	154 (0.70)	12 (1.55)	47 (0.78)	3075 (0.46)
20 to 24 years	608 (9.11)	1682 (7.60)	76 (9.81)	551 (9.17)	39967 (5.94)
25 to 29 years	1441 (21.59)	4662 (21.07)	169 (21.81)	1341 (22.32)	140692 (20.91)
30 to 34 years	2054 (30.78)	6823 (30.84)	216 (27.87)	1889 (31.45)	228521 (33.96)
35 to 39 years	1522 (22.80)	5248 (23.72)	175 (22.58)	1353 (22.52)	162895 (24.21)
≥ 40 years	1003 (15.03)	3556 (16.07)	127 (16.39)	826 (13.75)	97719 (14.52)
Education					
Primary and lower secondary, < 9 years	126 (1.89)	305 (1.38)	22 (2.84)	115 (1.91)	14398 (2.14)
Primary and lower secondary, 9 years	847 (12.69)	2612 (11.81)	108 (13.94)	724 (12.05)	60713 (9.02)
Upper secondary, 1-2 years	1241 (18.59)	4347 (19.65)	158 (20.39)	1110 (18.48)	113241 (16.83)
Upper secondary, 3 years	2076 (31.11)	6938 (31.36)	236 (30.45)	1996 (33.23)	202769 (30.13)
Post-secondary, < 3 years	864 (12.95)	2880 (13.02)	100 (12.90)	759 (12.64)	94803 (14.09)
Post-secondary, ≥ 3 years	1452 (21.76)	4731 (21.38)	139 (17.94)	1227 (20.43)	174698 (25.96)
Postgraduate	68 (1.02)	312 (1.41)	12 (1.55)	76 (1.27)	12247 (1.82)
Nationality (Swedish)	5491 (82.27)	18855 (85.22)	559 (72.13)	4960 (82.57)	527930 (78.46)
Criminal convictions (any)	2614 (39.17)	8608 (38.91)	333 (42.97)	2285 (38.04)	216113 (32.12)
Severe psychiatric problem[c]	74 (1.11)	289 (1.31)	8 (1.03)	87 (1.45)	3244 (0.48)
Suicide attempt (definite or uncertain)	416 (6.23)	1282 (5.79)	56 (7.23)	312 (5.19)	25835 (3.84)

All percentages are based on the number of offspring. [a]Age 6 Kaplan Meier estimates. [b]Year of birth is presented in bins in sTable II.6 but was not binned when used as a covariate in models. [c]Severe psychiatric problem was defined as an inpatient or outpatient diagnosis of schizophrenia, bipolar disorder, or other non-drug induced psychosis.

sTable II.7. Descriptive statistics stratified by paternal first-trimester dispensations of any antidepressants

	1st-trimester dispensations (n=18,727)	**No dispensations before, during, or after pregnancy** (n= 675,620)
	No. (%)	**No. (%)**
Offspring outcomes		
Preterm birth	992 (5.30)	32024 (4.74)
Small for gestational age	423 (2.26)	14623 (2.16)
Autism spectrum disorder[a]	77 (0.81)	2125 (0.61)
Attention-deficit/hyperactivity disorder[a]	49 (0.68)	972 (0.36)
Pregnancy covariates		
First born	7893 (42.15)	301793 (44.67)
Second born	6554 (35.00)	252447 (37.37)
Third born	2833 (15.13)	87218 (12.91)
Fourth born or higher	1447 (7.73)	34162 (5.06)
Born 2006 to 2009[b]	10064 (53.74)	381620 (56.48)
Born 2010 to 2012[b]	8663 (46.26)	294000 (43.52)
Maternal covariates		
Age at birth		
< 20 years	309 (1.65)	9583 (1.42)
20 to 24 years	2195 (11.72)	85688 (12.68)
25 to 29 years	4955 (26.46)	195867 (28.99)
30 to 34 years	6373 (34.03)	237503 (35.15)
35 to 39 years	3971 (21.20)	121792 (18.03)
≥ 40 years	924 (4.93)	25187 (3.73)
Education		
Primary and lower secondary, < 9 years	600 (3.20)	16585 (2.45)
Primary and lower secondary, 9 years	1838 (9.81)	46592 (6.90)
Upper secondary, 1-2 years	2140 (11.43)	62703 (9.28)
Upper secondary, 3 years	5271 (28.15)	191879 (28.40)
Post-secondary, < 3 years	2305 (12.31)	85920 (12.72)
Post-secondary, ≥ 3 years	6374 (34.04)	263433 (38.99)
Postgraduate	199 (1.06)	8508 (1.26)
	14604 (77.98)	534445 (79.10)
	2586 (13.81)	65127 (9.64)
Nationality (Swedish)	379 (2.02)	5393 (0.80)
Criminal convictions (any)	1192 (6.37)	27118 (4.01)
Severe psychiatric problem[c]		
Suicide attempt (definite or uncertain)		
	83 (0.44)	3158 (0.47)
Paternal covariates		
Age at birth	844 (4.51)	40960 (6.06)
< 20 years	3099 (16.55)	142359 (21.07)
20 to 24 years	5746 (30.68)	229720 (34.00)
25 to 29 years	4980 (26.59)	162975 (24.12)
30 to 34 years	3975 (21.23)	96448 (14.28)
35 to 39 years		
≥ 40 years	474 (2.53)	13993 (2.07)
Education	2640 (14.10)	59944 (8.87)

Primary and lower secondary, < 9 years	**1st-trimester dispensations** (n=18,727)	**No dispensations before, during, or after pregnancy** (n= 675,620)
Primary and lower secondary, 9 years	**No. (%)**	**No. (%)**
Upper secondary, 1-2 years	3871 (20.67)	113159 (16.75)
Upper secondary, 3 years	4931 (26.33)	205399 (30.40)
Post-secondary, < 3 years	2347 (12.53)	95382 (14.12)
Post-secondary, ≥ 3 years	4156 (22.19)	175515 (25.98)
Postgraduate	308 (1.64)	12228 (1.81)
Nationality (Swedish)	14870 (79.40)	532719 (78.85)
Criminal convictions (any)	8514 (45.46)	214354 (31.73)
Severe psychiatric problem[c]	978 (5.22)	2142 (0.32)
Suicide attempt (definite or uncertain)	1808 (9.65)	24632 (3.65)

All percentages are based on the number of offspring. [a]Age 6 Kaplan Meier estimates. [b]Year of birth is presented in bins in sTable II.7 but was not binned when used as a covariate in models. [c]Severe psychiatric problem was defined as an inpatient or outpatient diagnosis of schizophrenia, bipolar disorder, or other non-drug induced psychosis.

sTable II.8. Descriptive statistics stratified by paternal first-trimester dispensations of SSRIs

	1st-trimester dispensations (n=13,521)	**No dispensations before, during, or after pregnancy** (n=684,714)
	No. (%)	**No. (%)**
Offspring outcomes		
Preterm birth	720 (5.33)	32486 (4.74)
Small for gestational age	291 (2.15)	14851 (2.17)
Autism spectrum disorder[a]	55 (0.75)	2157 (0.61)
Attention-deficit/hyperactivity disorder[a]	37 (0.67)	994 (0.36)
Pregnancy covariates		
First born	5754 (42.56)	305525 (44.62)
Second born	4776 (35.32)	255557 (37.32)
Third born	2032 (15.03)	88602 (12.94)
Fourth born or higher	959 (7.09)	35030 (5.12)
Born 2006 to 2009[b]	7252 (53.64)	386666 (56.47)
Born 2010 to 2012[b]	6269 (46.36)	298048 (43.53)
Maternal covariates		
Age at birth		
< 20 years	222 (1.64)	9756 (1.42)
20 to 24 years	1496 (11.06)	87065 (12.72)
25 to 29 years	3616 (26.74)	198353 (28.97)
30 to 34 years	4675 (34.58)	240266 (35.09)
35 to 39 years	2859 (21.14)	123621 (18.05)
≥ 40 years	653 (4.83)	25653 (3.75)
Education		
Primary and lower secondary, < 9 years	347 (2.57)	17032 (2.49)
Primary and lower secondary, 9 years	1216 (8.99)	47800 (6.98)
Upper secondary, 1-2 years	1471 (10.88)	63936 (9.34)
Upper secondary, 3 years	3816 (28.22)	194470 (28.40)
Post-secondary, < 3 years	1656 (12.25)	86992 (12.70)
Post-secondary, ≥ 3 years	4873 (36.04)	265887 (38.83)
Postgraduate	142 (1.05)	8597 (1.26)
	10890 (80.54)	540855 (78.99)
	1756 (12.99)	66667 (9.74)
Nationality (Swedish)	248 (1.83)	5608 (0.82)
Criminal convictions (any)	839 (6.21)	27761 (4.05)
Severe psychiatric problem[c]		
Suicide attempt (definite or uncertain)		
	67 (0.50)	3201 (0.47)
Paternal covariates		
Age at birth	608 (4.50)	41491 (6.06)
< 20 years	2300 (17.01)	143887 (21.01)
20 to 24 years	4284 (31.68)	232237 (33.92)
25 to 29 years	3649 (26.99)	165167 (24.12)
30 to 34 years	2613 (19.33)	98731 (14.42)
35 to 39 years		
≥ 40 years	270 (2.00)	14374 (2.10)
Education	1764 (13.05)	61624 (9.00)
Primary and lower secondary, < 9 years	2705 (20.01)	115293 (16.84)

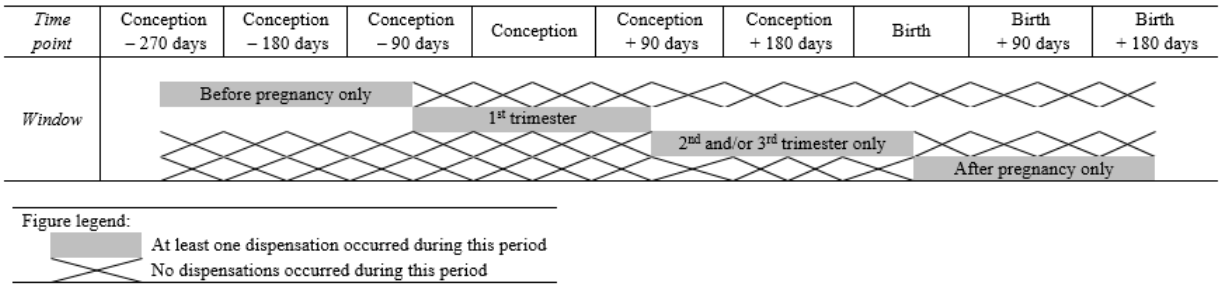
	1st-trimester dispensations (n=13,521)	**No dispensations before, during, or after pregnancy** (n=684,714)
Primary and lower secondary, 9 years	**No. (%)**	**No. (%)**
Upper secondary, 1-2 years	3658 (27.05)	207594 (30.32)
Upper secondary, 3 years	1692 (12.51)	96471 (14.09)
Post-secondary, < 3 years	3199 (23.66)	177024 (25.85)
Post-secondary, ≥ 3 years	233 (1.72)	12334 (1.80)
Postgraduate	11062 (81.81)	539150 (78.74)
Nationality (Swedish)	5885 (43.52)	219182 (32.01)
Criminal convictions (any)	620 (4.59)	2634 (0.38)
Severe psychiatric problem[c]	1126 (8.33)	25773 (3.76)
Suicide attempt (definite or uncertain)		

All percentages are based on the number of offspring. [a]Age 6 Kaplan Meier estimates. [b]Year of birth is presented in bins in sTable II.8 but was not binned when used as a covariate in models. [c]Severe psychiatric problem was defined as an inpatient or outpatient diagnosis of schizophrenia, bipolar disorder, or other non-drug induced psychosis.

sTable II.9. Adjusted associations between maternal antidepressant dispensations before pregnancy, during the first trimester of pregnancy, during the second and/or third trimester of pregnancy, and after pregnancy and offspring birth and neurodevelopmental outcomes

	Four parameter model estimates								Model fit	
	1. Before pregnancy		2. 1st trimester		3. 2nd and/or 3rd trimester		4. After pregnancy		Four Parameter model	Parameters 1 and 2 constrained to equality
Any antidepressant										
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**AIC**	**AIC**
PTB	1.17	1.07-1.28	1.40	1.33-1.47	1.15	0.84-1.57	1.34	1.21-1.48	268512.64	268522.38
SGA	1.07	0.93-1.24	1.12	1.03-1.21	1.17	0.75-1.84	1.05	0.89-1.24	143724.04	143722.26
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**AIC**	**AIC**
ASD	1.40	1.02-1.93	1.75	1.49-2.07	2.18	0.98-4.85	1.45	1.03-2.04	65876.69	65876.32
ADHD	2.09	1.53-2.86	1.85	1.55-2.20	0.24	0.06-1.01	1.86	1.39-2.48	46856.51	46854.97
SSRIs										
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**AIC**	**AIC**
PTB	1.13	1.02-1.25	1.37	1.30-1.45	1.06	0.77-1.45	1.31	1.18-1.46	268561.62	268570.72
SGA	1.09	0.94-1.28	1.13	1.03-1.23	1.17	0.76-1.82	1.01	0.85-1.21	143723.97	143722.08
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**AIC**	**AIC**
ASD	1.49	1.06-2.10	1.72	1.43-2.06	2.13	0.96-4.76	1.64	1.17-2.29	65881.61	65880.16
ADHD	1.93	1.35-2.74	1.81	1.50-2.19	0.50	0.17-1.42	1.86	1.37-2.52	46876.16	46874.25

OR=odds ratio. HR=hazard ratio. CI=confidence interval. PTB=preterm birth. SGA=small for gestational age. ASD=autism spectrum disorder. ADHD=attention deficit/hyperactivity disorder. Models were fit in a sample of 708,450 offspring. The four parameter model included the following four parameters that compared the following groups to offspring unexposed to any antidepressants: (1) dispensations only before pregnancy, (2) dispensations for the first trimester of pregnancy, (3) dispensations only for the second and/or third trimester of pregnancy, and (4) dispensations only after pregnancy. Models also controlled for parity and year of birth and maternal and paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts. Models were compared using the Akaike information criterion (AIC).



sFigure II.1. Dispensation windows. The before-pregnancy-only window included offspring of women who were dispensed antidepressants in the period 270 days before conception to 90 days before conception but were not dispensed antidepressants in the period 90 days before conception to 180 days after birth. The 1st-trimester window included offspring of women who were dispensed antidepressants in the period 90 days before conception to 90 days after conception. Offspring of women who were also dispensed antidepressants before or after the defined exposure window were considered exposed in the 1st-trimester window. The 2nd- and/or 3rd-trimester only window included offspring of women who were dispensed antidepressants in the period 90 days after conception to birth but were not dispensed antidepressants in the period 270 days before conception to 90 days after conception and were not dispensed antidepressants in the period 180 days after birth. The after pregnancy only window included offspring of women who were dispensed antidepressants in the period 180 days after birth but were not dispensed antidepressants in the period 270 days before conception through birth.

SII.3 Appendix: Test of Exposure Misclassification

In the sample of 708,450 offspring born between 2006 and 2012, maternal self-report data on antidepressant use was used in combination with maternal antidepressant dispensation data to evaluate whether exposure misclassification may have biased the results.

The main analyses used two different definitions for first-trimester antidepressant exposure. First-trimester exposure was defined (a) according to maternal self-reports and (b) according to dispensation data. Women self-reported antidepressant use at the first antenatal visit, which typically occur between the 10^{th} and 12^{th} week of pregnancy. First-trimester exposure based on dispensation records was defined as having at least one dispensation between 90 days before estimated conception and 90 days after estimated conception. (sFigure II.1 shows a diagram of exposure windows.)

To test for biases from exposure misclassification, we first calculated kappa estimates to assess agreement between the two exposures definitions used in the main analyses.

Then, four additional exposure definitions were created.

The first definition classified cases as exposed if *either* exposure definition used in the main analyses indicated exposure. According to this definition, 28,158 (4.0% of the 2006-2012 cohort) offspring were exposed to any antidepressant, and 23,422 (3.3%) offspring were exposed to SSRIs specifically.

The second definition classified cases as exposed if *both* exposure definitions used in the main analyses indicated exposure. According to this definition, 13,435 (1.9%) offspring were exposed to any antidepressant, and 11,516 (1.6%) offspring were exposed to SSRIs specifically.

The third definition used a narrower window than the main analyses' first-trimester dispensation definition. Specifically, it defined exposure as having at least one dispensation between *30* days before estimated conception and 90 days after estimated conception. According

to this definition, 7,455 (1.1%) offspring were exposed to any antidepressant, and 5,593 (0.8%) offspring were exposed to SSRIs specifically.

The fourth definition required at least *two* dispensations in the dispensation window used in the main analyses (between 90 days before estimated conception and 90 days after estimated conception). According to this definition, 14,288 (2.0%) offspring were exposed to any antidepressant, and 11,333 (1.6%) offspring were exposed to SSRIs specifically.

Models assessing associations between the four additional definitions of exposure and offspring problems included pregnancy-related, maternal, and paternal covariates.

In general, the results from the sensitivity analyses suggest that exposure misclassification and self-report biases did not influence the results.

Maternal reports and dispensation records showed substantial agreement (kappa=0.64, 95% CI [0.63 to 0.64] for any antidepressant, and kappa=0.65, 95% CI [0.65 to 0 .66] for SSRIs). Additionally, commensurate associations were found across the two exposure definitions used in the main paper and the four additional definitions described here (Table 2, Table 3, sTable II.10).

sTable II.10. Adjusted associations between four definitions of first-trimester antidepressant use and offspring birth and neurodevelopmental outcomes

	Exposure according to self-reported use *OR* dispensation data		Exposure according to self-report use *AND* dispensation data		Narrower first-trimester exposure dispensation window		Two dispensations during 1st trimester	
Any antidepressant								
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
PTB	1.38	1.31-1.45	1.40	1.31-1.50	1.44	1.36-1.52	1.54	1.41-1.68
SGA	1.12	1.03-1.21	1.13	1.01-1.26	1.14	1.04-1.25	1.13	0.98-1.31
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
ASD	1.71	1.46-2.01	1.83	1.46-2.28	1.85	1.54-2.22	1.72	1.28-2.31
ADHD	1.70	1.44-2.00	1.75	1.38-2.22	1.83	1.50-2.22	1.81	1.34-2.44
SSRIs								
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
PTB	1.34	1.27-1.42	1.34	1.24-1.44	1.42	1.34-1.51	1.45	1.31-1.61
SGA	1.12	1.03-1.22	1.13	1.01-1.28	1.17	1.06-1.29	1.17	0.99-1.38
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
ASD	1.71	1.44-2.04	1.75	1.37-2.24	1.83	1.50-2.24	1.71	1.21-2.41
ADHD	1.62	1.35-1.95	1.76	1.36-2.28	1.87	1.51-2.31	1.83	1.29-2.58

OR=odds ratio. HR=hazard ratio. CI=confidence interval. PTB=preterm birth. SGA=small for gestational age. ASD=autism spectrum disorder. ADHD=attention deficit/hyperactivity disorder. Models were fit in a sample of 708,450 offspring. Models controlled for parity and year of birth and maternal and paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts.

SII.4 Appendix: Test of Generalizability of Sibling Comparisons

An assumption of sibling comparisons is that results will generalize to other samples (e.g., families with only one child, families without variability in the outcome). An additional analysis was conducted to test this assumption. Specifically, given that families with single included offspring were excluded from sibling comparison analyses (because they cannot provide information), we assessed baseline and adjusted associations in a subsample of 1,139,753 offspring who had at least one sibling in the dataset in order to assess the generalizability of the sibling comparison results. Although associations with small for gestational age were not statistically significant, the general pattern of results were consistent with findings from the main analyses (sTable II.11), suggesting that reduction in the effect sizes in the sibling-comparison models, particularly for the neurodevelopmental outcomes, was not due to the exclusion of single-offspring families.

sTable II.11. Baseline and adjusted associations between maternal self-reported first-trimester antidepressant use and offspring birth and neurodevelopmental outcomes in multiple-offspring families

	Baseline Model		Adjusted Model	
Any antidepressant				
	OR	**95% CI**	**OR**	**95% CI**
PTB	1.48	1.38-1.58	1.37	1.28-1.47
SGA	1.06	0.94-1.20	1.06	0.94-1.19
	HR	**95% CI**	**HR**	**95% CI**
ASD	2.08	1.80-2.39	1.70	1.47-1.96
ADHD	2.09	1.89-2.31	1.48	1.34-1.64
SSRIs				
	OR	**95% CI**	**OR**	**95% CI**
PTB	1.39	1.29-1.50	1.29	1.20-1.39
SGA	1.03	0.90-1.18	1.03	0.90-1.18
	HR	**95% CI**	**HR**	**95% CI**
ASD	2.06	1.75-2.42	1.69	1.44-1.99
ADHD	2.18	1.94-2.44	1.54	1.37-1.73

OR=odds ratio. HR=hazard ratio. CI=confidence interval. PTB=preterm birth. SGA=small for gestational age. ASD=autism spectrum disorder. ADHD=attention deficit/hyperactivity disorder. All models were fit in a sample of 1,139,753 offspring who had at least one sibling in the dataset. Baseline models controlled for parity and year of birth. Adjusted models controlled for parity and year of birth and maternal and paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts.

SII.5 Appendix: Test of Confounding from Exposure to Other Psychotropic Medications

Offspring with maternal self-reported first-trimester exposure to other psychotropic medications, defined as antiepileptic medications, antipsychotic medications, medications used to treat addictive disorders, anxiolytics, attention-deficit/hyperactivity disorder medication, and opioid analgesics, were identified (sTable II.12 lists specific drug names and Anatomical Therapeutic Chemical Classification [ATC] codes). Given that 9.8% (2,204) of offspring exposed to antidepressants were also exposed to other psychotropic medications, associations between maternal self-reported first-trimester antidepressant use and offspring outcomes were assessed in a subsample of 1,563,250 offspring who were not exposed to the other psychotropic medications. These associations were commensurate to associations observed in the main analyses (sTable II.13), suggesting that exposure to other psychotropic medications did not bias the results.

sTable II.12. Drug names and Anatomical Therapeutic Chemical Classification codes for other psychotropic medications

ATC code	Medication name
Antiepileptic medications	
N03AA01	methylphenobarbital
N03AA02	phenobarbital
N03AA03	primidone
N03AA04	barbexaclone
N03AA30	metharbital
N03AB01	ethotoin
N03AB02	phenytoin
N03AB03	amino(diphenylhydantoin) valeric acid
N03AB04	mephenytoin
N03AB05	fosphenytoin
N03AB52	phenytoin, combinations
N03AB54	mephenytoin, combinations
N03AC01	paramethadione
N03AC02	trimethadione
N03AC03	ethadione
N03AD01	ethosuximide
N03AD02	phensuximide
N03AD03	mesuximide
N03AD51	ethosuximide, combinations
N03AF01	carbamazepine
N03AF02	oxcarbazepine
N03AF03	rufinamide
N03AF04	eslicarbazepine
N03AG01	valproic acid
N03AG02	valpromide
N03AG03	aminobutyric acid
N03AG04	vigabatrin
N03AG05	progabide
N03AG06	tiagabine
N03AX03	sultiame
N03AX07	phenacemide
N03AX09	lamotrigine
N03AX10	felbamate
N03AX11	topiramate
N03AX12	gabapentin
N03AX13	pheneturide
N03AX14	levetiracetam
N03AX15	zonisamide
N03AX16	pregabalin
ATC code	**Medication name**
Antiepileptic medications	
N03AX17	stiripentol
N03AX18	lacosamide
N03AX19	carisbamate
N03AX21	retigabine
N03AX22	perampanel
N03AX30	beclamide
N05AN01	lithium
Antipsychotic medications	
N05AA01	chlorpromazine
N05AA02	levomepromazine

N05AA03	promazine
N05AA04	acepromazine
N05AA05	triflupromazine
N05AA06	cyamemazine
N05AA07	chlorproethazine
N05AB01	dixyrazine
N05AB02	fluphenazine
N05AB03	perphenazine
N05AB04	prochlorperazine
N05AB05	thiopropazate
N05AB06	trifluoperazine
N05AB07	acetophenazine
N05AB08	thioproperazine
N05AB09	butaperazine
N05AB10	perazine
N05AC01	periciazine
N05AC02	thioridazine
N05AC03	mesoridazine
N05AD01	haloperidol
N05AD02	trifluperidol
N05AD03	melperone
N05AD04	moperone
N05AD05	pipamperone
N05AD06	bromperidol
N05AD07	benperidol
N05AD08	droperidol
N05AD09	fluanisone
N05AE01	oxypertine
N05AE02	molindone
N05AE03	sertindole
N05AE04	ziprasidone
ATC code	**Medication name**
Antipsychotic medications	
N05AE05	lurasidone
N05AF01	flupentixol
N05AF02	clopenthixol
N05AF03	chlorprothixene
N05AF04	tiotixene
N05AF05	zuclopenthixol
N05AG01	fluspirilene
N05AG02	pimozide
N05AG03	penfluridol
N05AH01	loxapine
N05AH02	clozapine
N05AH03	olanzapine
N05AH04	quetiapine
N05AH05	asenapine
N05AH06	clotiapine
N05AL01	sulpiride
N05AL02	sultopride
N05AL03	tiapride
N05AL04	remoxipride
N05AL05	amisulpride
N05AL06	veralipride
N05AL07	levosulpiride
N05AX07	prothipendyl

N05AX08	risperidone
N05AX10	mosapramine
N05AX11	zotepine
N05AX12	aripiprazole
N05AX13	paliperidone
N05AX14	iloperidone
Medications for addictive disorders	
N07BA01	nicotine
N07BA03	varenicline
N07BB01	disulfiram
N07BB02	calcium carbimide
N07BB03	acamprosate
N07BB04	naltrexone
N07BC01	buprenorphine
N07BC02	methadone
N07BC03	levacetylmethadol
N07BC04	lofexidine
N07BC05	levomethadone
ATC code	**Medication name**
Medications for addictive disorders	
N07BC06	diamorphine
N07BC51	buprenorphine, combinations
Anxiolytics	
N03AE01	clonazepam
N05BA01	diazepam
N05BA02	chlordiazepoxide
N05BA04	oxazepam
N05BA05	clorazepate
N05BA06	lorazepam
N05BA12	alprazolam
N05CD01	flurazepam
N05CD04	estazolam
N05CD05	triazolam
N05CD07	temazepam
N05CD08	midazolam
N05CD1l0	quazepam
N05BE01	buspirone
N05BB01	atarax
N05BB01	vistaril
Attention-deficit/hyperactivity disorder medications	
N06BA01	amfetamine
N06BA02	dexamfetamine
N06BA04	methylphenidate
N06BA09	atomoxetine
Opioids	
N02AA01	Morphine
N02AA03	Hydromorphine
N02AA05	Oxycodone
N02AA55	Oxycodone/nalaxone
N02AA59	Codeine excl. psychotropics
N02AB01	Ketobemidone
N02AB02	Pethidine
N02AB03	Fentanyl
N02AC04	Dextropropoxyphene
N02AC54	Dextropropoxyphene excl psycholeptics

N02AD01	Pentazocine
N02AE01	Buprenorphine
N02AG01	Morphine & antispasmodics
N02AG02	Ketobemidone/ dimethylaminophenylbutene
N02AG04	Hydromorphone & antispasmodics
ATC code	**Medication name**
Opioids	
N02AX02	Tramadol

ATC=Anatomical Therapeutic Chemical Classification

sTable II.13. Baseline, adjusted, and sibling comparison associations between maternal self-reported first-trimester antidepressant use and offspring birth and neurodevelopmental outcomes in a subsample of offspring *not exposed* to other psychotropic medications

	Baseline Model		Adjusted Model		Sibling Comparison	
Any antidepressant						
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
PTB	1.40	1.32-1.48	1.30	1.22-1.37	1.30	1.13-1.49
SGA	1.12	1.03-1.23	1.11	1.02-1.22	0.92	0.73-1.17
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
ASD	1.85	1.64-2.10	1.53	1.35-1.74	0.67	0.48-0.94
ADHD	2.16	1.99-2.35	1.58	1.46-1.72	1.02	0.79-1.30
SSRIs						
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
PTB	1.31	1.23-1.40	1.22	1.15-1.30	1.27	1.10-1.48
SGA	1.08	0.98-1.20	1.08	0.98-1.20	0.82	0.63-1.06
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
ASD	1.85	1.61-2.13	1.53	1.33-1.76	0.67	0.46-0.97
ADHD	2.17	1.98-2.39	1.58	1.44-1.74	0.96	0.73-1.27

OR=odds ratio. HR=hazard ratio. CI=confidence interval. PTB=preterm birth. SGA=small for gestational age. ASD=autism spectrum disorder. ADHD=attention deficit/hyperactivity disorder. Baseline and adjusted models were fit in a sample of 1,563,250 offspring. Baseline models controlled for parity and year of birth. Adjusted models controlled for parity and year of birth and maternal and paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts. Sibling comparisons controlled for parity and year of birth, paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts, and maternal age at childbearing.

SII.6 Appendix: Test of Bias from Left Censoring

Given that, prior to 2001, outpatient psychiatric diagnoses were not included in the National Patient Register, we conducted analyses in a sample of 1,162,873 offspring born in 2001 or later to assess whether left censoring of the neurodevelopmental outcomes may have biased the results. The analyses also enabled us to examine whether cohort effects influenced the results. These analyses assessed associations between maternal self-reported first-trimester antidepressant use and offspring autism spectrum disorder and attention-deficit/hyperactivity disorder in baseline, adjusted, and sibling comparison models. The results were commensurate to the main analyses (sTable II.14), suggesting that left censoring of the outcomes and cohort effects did not influence the results.

sTable II.14. Baseline, adjusted, and sibling comparison associations between maternal self-reported first-trimester antidepressant use and offspring neurodevelopmental outcomes in a subsample born in 2001 or after

	Baseline Model		Adjusted Model		Sibling Comparison	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Any antidepressant						
ASD	2.04	1.79-2.32	1.71	1.49-1.95	0.88	0.59-1.33
ADHD	2.29	2.09-2.52	1.63	1.48-1.80	1.05	0.73-1.50
SSRIs						
ASD	2.06	1.78-2.38	1.75	1.51-2.02	0.90	0.58-1.40
ADHD	2.28	2.05-2.53	1.63	1.46-1.81	0.92	0.62-1.35

HR=hazard ratio. CI=confidence interval. PTB=preterm birth. SGA=small for gestational age. ASD=autism spectrum disorder. ADHD=attention deficit/hyperactivity disorder. Baseline and adjusted models were fit in a sample of 1,162,873 offspring. Baseline models controlled for parity and year of birth. Adjusted models controlled for parity and year of birth and maternal and paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts. Sibling comparisons controlled for parity and year of birth, paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts, and maternal age at childbearing.

SII.7 Appendix: Test of Validity of Early Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder Diagnoses

There is uncertainty about the stability over time of early neurodevelopmental disorder diagnoses.[e.g.,1] Thus, we conducted a sensitivity analyses to test the validity of early autism spectrum disorder and attention-deficit/hyperactivity disorder diagnoses. Offspring diagnosed before the age of 2 were excluded from the sample and baseline, adjusted, and sibling comparison associations were re-examined. Associations with autism spectrum disorder were assessed in a sample of 1,580,430 offspring. Associations with attention-deficit/hyperactivity disorder were assessed in a sample of 1,580,509 offspring. Associations were commensurate to main analyses associations (sTable II.15), suggesting that early neurodevelopmental diagnoses of potentially questionable validity did not bias the results.

sTable II.15. Baseline, adjusted, and sibling comparison associations between maternal self-reported first-trimester antidepressant use and offspring neurodevelopmental outcomes in a sample excluding offspring diagnosed before age 2 years

	Baseline Model		Adjusted Model		Sibling Comparison	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Any antidepressant						
ASD	2.01	1.80-2.26	1.63	1.45-1.83	0.83	0.61-1.13
ADHD	2.21	2.04-2.38	1.58	1.46-1.71	1.00	0.79-1.26
SSRIs						
ASD	2.03	1.79-2.31	1.65	1.45-1.88	0.81	0.57-1.14
ADHD	2.25	2.06-2.46	1.60	1.46-1.75	0.95	0.73-1.23

HR=hazard ratio. CI=confidence interval. ASD=autism spectrum disorder. ADHD=attention deficit/hyperactivity disorder. Baseline and adjusted associations with autism spectrum disorder were assessed in a sample of 1,580,430 offspring. Baseline and adjusted associations with attention-deficit/hyperactivity disorder were assessed in a sample of 1,580,509 offspring. Adjusted models controlled for parity and year of birth and maternal and paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts. Sibling comparisons controlled for parity and year of birth, paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts, and maternal age at childbearing.

Reference

1. Turner LM, Stone WL. Variability in outcome for children with an ASD diagnosis at age 2. *J Child Psychol Psychiatry.* 2007;48(8):793-802.

SII.8 Appendix: Examining Associations Between Dispensations During Later Pregnancy and Offspring Outcomes Among Those with a First-trimester Dispensation

Given that the main analyses focused on first-trimester antidepressant exposure, we conducted a sensitivity analysis to explore whether continued dispensations in the second and/or third trimester was associated with the birth and neurodevelopmental outcomes compared to dispensations only during the first trimester. We defined a group of offspring, labeled Continuers, as those whose mothers had a first-trimester dispensation *and* a second- or third-trimester dispensation. We defined a second group, labeled Discontinuers, as offspring whose mothers had a first-trimester dispensation but not a second- or third-trimester dispensation. Of the 26,477 offspring in the cohort with first-trimester dispensations, 12,291 (46%) were Continuers and 14186 (54%) were Discontinuers. Of the 22,125 offspring with first-trimester dispensations of SSRI specifically, 10,757 (49%) were continuers and 11,368 (51%) were discontinuers.

We examined adjusted associations between continuation of use late in pregnancy and the birth and neurodevelopmental outcomes (sTable II.16). The association between continued dispensations of antidepressants and preterm birth (OR=1.4, 95% CI [1.3, 1.6]) and small for gestational age (OR=1.2, 95% CI [1.0, 1.4] were statistically significant. The association with autism spectrum disorder was moderate in magnitude (HR=1.3, 95% CI [1.0, 1.8]), though not statistically significant. Continuation of dispensations was associated with a moderate decrease in the risk for attention-deficit/hyperactivity disorder (HR=0.8, 95% CI [0.5, 1.1]), but the association was not statistically significant.

These analyses cannot differentiate whether the associations were due to increased severity of depression (i.e., confounding by indication severity) or the intrauterine exposure to antidepressants later in pregnancy.

sTable II.16. Adjusted associations between continuation of antidepressant dispensations late in pregnancy and offspring birth and neurodevelopmental outcomes among those with a first-trimester dispensation

	Adjusted Model	
Any antidepressant		
	OR	**95% CI**
PTB	1.44	1.30-1.59
SGA	1.18	1.01-1.39
	HR	**95% CI**
ASD	1.32	0.96-1.81
ADHD	0.76	0.53-1.08
SSRIs		
	OR	**95% CI**
PTB	1.39	1.24-1.54
SGA	1.21	1.01-1.44
	HR	**95% CI**
ASD	1.22	0.86-1.74
ADHD	0.71	0.47-1.06

OR=odds ratio. HR=hazard ratio. CI=confidence interval. PTB=preterm birth. SGA=small for gestational age. ASD=autism spectrum disorder. ADHD=attention deficit/hyperactivity disorder. Models predicting outcomes from any antidepressant dispensation were fit in a sample of 26,477 offspring. Models predicting outcomes from SSRIs dispensation were fit in a sample of 22,125 offspring. Models controlled for parity and year of birth and maternal and paternal country of birth, age at childbearing, highest level of completed education, history of any criminal convictions, history of severe psychiatric problems, and history of any suicide attempts.

III. Paper 2:

Maternal prescribed opioid analgesic use during pregnancy and associations with adverse birth outcomes: A population-based study

Citation:

Sujan, A.C., Quinn, P.D., Rickert, M.E., Wiggs, K.K., Lichtenstein, P., Larsson, H., Almqvist, C, Oberg, A.S., D'Onofrio, B.M. (2019). Maternal prescribed opioid analgesic use during pregnancy and associations with adverse birth outcomes: A population-based study. *PLOS Medicine, 16(12): e1002980.* doi: 10.1371/journal.pmed.1002980. PMID: 31790390.

Abstract

Background: Published research on prescribed opioid analgesic (POA) use during pregnancy and birth outcomes is limited in scope and has not adequately adjusted for potential confounding factors. To help address these gaps, we estimated associations between maternal POAs during pregnancy and two adverse birth outcomes using a large population-based dataset, multiple definitions of POA exposure, and several methods to evaluate the influence of both measured and unmeasured confounding factors.

Methods and Findings: We obtained data by linking information from several Swedish registers and conducted a retrospective cohort study on a population-based sample of 620,458 Swedish births occurring between 2007 and 2013 (48.6% female; 44.4% first born).

We evaluated associations between prenatal POA exposure and risk for preterm birth (PTB; <37 gestational weeks) and small for gestational age (SGA; birth weight more than 2 standard deviations below the expected weight for gestational age). We evaluated the influence of confounding by adjusting for a wide range of measured covariates while comparing exposed and unexposed infants. Additionally, we adjusted for unmeasured confounding factors by using several advanced epidemiological designs.

Infants exposed to POAs anytime during pregnancy were at increased risk for PTB compared to unexposed infants (6.4% exposed versus 4.4% unexposed; adjusted odds ratio [OR]=1.38, 95% confidence interval [CI]:1.31-1.45, $p<0.001$). This association was attenuated when we compared POA-exposed infants to acetaminophen-exposed infants (OR=1.18, 95% CI:1.07-1.30, $p<0.001$), infants born to women who used POAs before pregnancy only (OR=1.05, 95% CI:0.96-1.14, $p=0.27$), and unexposed siblings (OR=0.99, 95% CI:0.85-1.14, $p=0.92$). We also evaluated associations with short-term versus persistent POA use during

pregnancy and observed a similar pattern of results, though the magnitudes of associations with persistent exposure were larger than associations with any use or short-term use.

Although short-term use was not associated with SGA (adjusted $OR_{single\text{-}trimester}$=0.95, 95% CI:0.87-1.04, p=0.29), persistent use was associated with increased risk for SGA (adjusted $OR_{multiple\text{-}trimester}$=1.40, 95% CI:1.17-1.67, p<0.001) compared to unexposed infants. The association with persistent exposure was attenuated when we used alternative comparison groups (e.g., sibling comparison OR=1.22, 95% CI:0.60-2.48, p=0.58).

Of note, our study had limitations, including potential bias from exposure misclassification, an inability to adjust for all sources of confounding, and uncertainty regarding generalizability to countries outside of Sweden.

Conclusions: Our results suggested that observed associations between POA use during pregnancy and risk of PTB and SGA were largely due to unmeasured confounding factors, although we could not rule out small independent associations, particularly for persistent POA use during pregnancy.

Introduction

While estimates of the prevalence of opioid prescriptions among pregnant women vary across studies, research suggests that a substantial proportion of women are treated with opioids during pregnancy.[1-5] For example, a study of pregnant women enrolled in Medicare in the United States reported that 30% of pregnant women fill prescriptions for opioids.[5] Given that opioids cross the human placental barrier, maternal use of these medications results in fetal exposure.[6] However, effects of prenatal exposure to both illicit and prescription opioids on child development are unclear.[7-9] The existing research on opioid use during pregnancy has largely focused on illicit opioids (e.g., heroin) or buprenorphine and methadone in the context of medication-assisted treatment for opioid use disorder.[10-14] However, the use of prescribed opioid analgesics (POAs) for treatment of pain is much more common than illicit use of opioids[15] or medication-assisted treatment[16]. For example, approximately 5% of women use an illicit substance during pregnancy in the United States,[15] and less than 3% of women prescribed opioids are prescribed these medications to treat opioid use disorder.[16]

The limited research on POA use during pregnancy has focused on birth outcomes, particularly preterm birth (PTB), fetal growth, and structural birth defects,[7-9] all of which have potential consequences for future morbidity and mortality.[17-19] Some observational studies have reported statistically significant associations between prenatal POA exposure and birth outcomes, whereas others have not.[7-9] Moreover, it is unclear if observed associations are due to causal effects of POA exposure or confounding from indications for maternal analgesic use (e.g., traumatic injury, acute or chronic inflammation, musculoskeletal or neuropathic pain) or other patient characteristics (e.g., psychiatric disorders, concurrent use of other psychiatric medication).[16,20-25] To help address these gaps, we estimated associations between maternal

POAs during pregnancy and PTB and small for gestational age (SGA; a proxy for fetal growth restriction) in a large, population-based dataset, using multiple definitions of POA exposure and several methods to evaluate the influence of both measured and unmeasured confounding factors. To our knowledge, no previous study has used methods to evaluate the influence of unmeasured confounding, which is critical because solely adjusting for measured characteristics is unlikely to adequately capture all sources of confounding.[26,27] Because no single observational method can account for all plausible confounding factors, we sought converging evidence from multiple comparisons to rigorously test causal hypotheses.[28-30] Specifically, we compared POA-exposed infants to infants exposed to acetaminophen (i.e., paracetamol), infants born to mothers with POA prescriptions before but not during pregnancy, and their unexposed siblings.

Methods

We conducted a retrospective cohort, complete-case analysis study on a population-based sample of 620,458 Swedish births from July, 1st 2007 to December 31st, 2013 who were not exposed to opioids for the treatment of opioid use disorder. We processed and analyzed data using SAS 9.4 and STATA 15.1. A STROBE checklist (SIII.1 Appendix) and a description of our planned analyses (SIII.2 Appendix) is included in the supplemental materials.

The institutional review board at Indiana University and the regional ethical review board in Stockholm, Sweden approved this study. The study used data available from national registers, and informed consent was not necessary.

We obtained data by linking information from several Swedish registers.[31] The Multi-Generation Register includes biological relationships for all individuals born from 1932 and residing in Sweden since 1961.[32] The Swedish Prescribed Drug Register includes records of filled medication prescriptions since July 2005.[33,34] The Medical Birth Register includes

information on 96-99% of births and pregnancy characteristics since 1973.[35-37] The National Patient Register includes diagnostic codes from all hospital admissions since 1987 and 80% of specialist outpatient care since 2001.[38,39] The National Crime Register includes criminal convictions since 1973.[40,41] The Education Register includes highest level of completed formal education.[42] The integrated database for labor market research includes annual socio-economic data for all individuals since 1990.[43]

Measures

Prescribed opioid analgesic (POA) exposures. SIII.3 Appendix provides detailed information on the included POAs, including frequencies of prescriptions of specific POA medications and information on type of clinic prescribing the medications. For example, while many prescriptions originated from obstetrics/gynecology and maternity care clinics, the majority of prescriptions originated from other types of clinics.

We included all prescriptions with Anatomical Therapeutic Chemical (ATC) codes beginning with N02A, acetaminophen/codeine combination medications with ATC code N02BE51, and buprenorphine (N02AE01, N07BC01, N07BC51) and methadone (N07BC02) prescribed as POAs. We distinguished buprenorphine and methadone for pain treatment versus opioid-use disorder treatment with criteria used in previous publications.[44,45]

We considered several exposure definitions using maternal POA prescriptions during non-overlapping windows of time (sFigure III.1 in SIII.3 Appendix). We defined these windows relative to approximated last menstrual period (LMP) and conception dates. Consistent with prior research [46], we first estimated LMP by subtracting gestational age (predominantly based on ultrasound measurements occurring the 18th to 20th week of pregnancy) from birth date and then estimated conception date by adding 14 days to LMP. Gestational age was predominantly based

on ultrasound measurements given that approximately 95% of all pregnant women in Sweden undergo at least one ultrasound.[47]

Before-pregnancy-only exposure included those with a prescription 360 days before conception to 91days before conception and no prescriptions 90 days before conception to birth.

Exposure during a *washout-period-only* (i.e., the period in which there would be ambiguity regarding whether a filled prescription would lead to use during pregnancy) included those with a prescription 90 days before conception to the day before conception and no prescriptions from conception to birth. We chose a 90-day window for the washout period because in Sweden the maximum amount of opioid medication dispensed is for a three month period [48]. Including the washout-period-only variable as a predictor in models prevented individuals who only had filled prescriptions that occurred shortly before pregnancy from being classified as either exposed or unexposed during pregnancy.

We defined *during-pregnancy* exposure as filled prescriptions anytime from conception to birth. We also used the timing of maternal prescriptions across trimesters to create proxies for *short-term use* (occurring in a single trimester) versus *persistent use* (occurring in multiple trimesters). Any use was the primary exposure, and secondary analyses examined whether associations differed by duration of use. We did not consider timing of exposure as defined by use in specific trimesters because preliminary analyses did not provide support for sensitive periods of exposure during pregnancy (SIII.4 Appendix). Specifically, these preliminary analyses showed that while the magnitude of the associations with first-trimester exposure only (conception to 89 days after LMP) were slightly larger than the magnitude of associations with second-trimester (90 to 179 days after LMP) or third-trimester (180 days after LMP to birth) exposure, the associations were not statistically significantly different for both PTB (p=0.25) and

SGA (p=0.54).

Active comparator medication exposure. We considered exposures to maternal acetaminophen (N02BE01) as prescriptions (1) anytime during pregnancy, (2) in a single trimester, and (3) in multiple trimesters. For all three exposures, we excluded individuals with maternal POA prescriptions anytime during pregnancy in order to capture acetaminophen-only exposure.

Covariates. Pregnancy-related characteristics included birth order, year of birth, maternal-reported smoking during the first trimester, and maternal prescriptions of other psychiatric medications during pregnancy (sTable III.3 in SIII.3 Appendix includes ATC codes).

We included maternal and paternal characteristics that were associated with subsequent receipt of POAs.[20,49] Specifically, maternal and paternal characteristics included pre-conception inpatient and outpatient diagnoses of opioid use disorder, non-opioid substance use disorder, schizophrenia or bipolar disorder, and definite or uncertain suicide attempts made according to International Classification of Disease (ICD) criteria; any pre-conception conviction of violent, non-violent, drug or alcohol, or driving-related crimes; age at child birth; highest level of education at year of birth; and country of origin.

Other familial and socio-economic characteristics included maternal reports of parents' cohabitating at birth, family-level income quintile at year of birth relative to the Swedish population in that year, and neighborhood deprivation score quintile at year of birth relative to the Swedish population in that year. Neighborhood deprivation score was based on a principal component analysis of several yearly indicators for small geographical areas constructed to delineate socially homogenous areas. The deprivation score for a given area incorporated the proportion of welfare recipients, unemployed individuals, immigrants, divorced individuals, and individuals with low educational attainment, as well as measures of residential mobility, crime

rates, and neighborhood disposable income.[50]

Outcomes. Outcomes were PTB (birth before 37 gestational weeks) and SGA (birth weight more than 2 standard deviations below the expected fetal weight for gestational age).

Associations between POA exposure and birth outcomes

We fit five logistic regression models estimating associations between POA exposure and birth outcomes in the analytic sample using robust standard errors to account for clustering of individuals within nuclear families bound by the same biological mothers (i.e., siblings). In all models we included washout-period-only POA exposure as a dummy code.

We first fit all models using POA exposure anytime during pregnancy as the predictor. Then, we re-estimated the models using single-trimester and multiple-trimester exposure as predictors. SIII.5 Appendix lists predictors and comparison groups for the main analytic models.

Population-wide associations comparing exposed to all unexposed infants. Models 1 and 2 estimated population-wide associations with POA exposure compared to unexposed infants. Model 1 (unadjusted) did not include any covariates. Model 2 (adjusted) included all measured characteristics as covariates in the regression models. We did not use propensity scores to adjust for measured characteristics because with a relatively limited number of covariates, propensity score methods make exactly as much adjustment as more traditional, outcome regression methods.[51] For the purpose of transparency, all parameter estimates from model 2 are listed in SIII.6 Appendix.

Associations using alternative comparison groups. Models 3 through 5 used alternative comparison groups consisting of infants likely to share some maternal characteristics with exposed infants. Model 3 (comparative safety)[52] compared POA-exposed infants to acetaminophen-only exposed infants to assess the relative safety of the two medications. Given

that both POAs and acetaminophen are prescribed for the treatment of pain, a null difference between POA-exposed and acetaminophen-exposed infants would indicate that POA use is as safe as a commonly used pain medication and provide support for confounding by indication.

Model 4 (before-pregnancy use)[53] compared infants exposed to POAs during pregnancy to infants born to women with POA prescriptions before but not during pregnancy. By design, model 4 accounted for all unmeasured factors shared by women who were prescribed POAs around the time of pregnancy. No association between during pregnancy exposure compared to exposure before pregnancy only would suggest that shared factors rather than a causal influence of intrauterine POA exposure is responsible for an observed increased occurrence in adverse birth outcomes among infants born to women who filled POA prescriptions during pregnancy.

Model 5 (sibling comparison)[54] compared POA-exposed infants to their siblings who were unexposed to POAs during pregnancy. By design, this within-family comparisons accounts for all unmeasured genetic and environmental factors that make siblings similar, including all familial factors that were stable across pregnancies. A lack of association in a sibling comparison would suggest that familial risk factors rather than a causal effect of POA exposure during pregnancy explain observed population-wide associations. In addition to adjusting for potential unmeasured confounding factors by design (i.e., factors shared by the comparison groups), models 3 through 5 also included all measured covariates that varied between comparison groups.

Sensitivity analyses

We also conducted several sensitivity analyses of our modeling assumptions and evaluated the extent to which the exposure and outcome definitions influenced the main analyses results (Appendix SIII.7 to SIII.13).

Bias from exposure definitions. First, to explore potential bias from exposure misclassification, we estimated population associations while adjusting for all the covariates using several different exposure definitions: (1) an expanded exposure window that included the 90 days before conception in case a prescription that was filled shortly before pregnancy was used during pregnancy, (2) a restricted exposure window that excluded the three days before birth in case a woman was prescribed POAs at the end of her pregnancy to use after delivery, and (3) an exposure defined according to filled prescriptions or maternal-reported use in order to capture women who filled POA prescription before pregnancy but used them during pregnancy (SIII.7 Appendix).

Second, to evaluate whether a specific type of POA medication was largely driving our findings, we re-estimated adjusted associations in (1) a subsample excluding births occurring to women with during pregnancy prescriptions of dextropropoxyphene (N02AC04 and N02AC54) because this medication is no longer prescribed in Sweden and (2) a subsample excluding births occurring to women with during pregnancy methadone or buprenorphine prescriptions in case these infants were exposed to prescribed opioids for the treatment of opioid use disorder rather than pain (SIII.8 Appendix).

Third, in order to evaluate if exposure to medications other than POAs that are included in POA combination medications influenced the main analyses result, we estimated adjusted associations in a subsample excluding births occurring to mothers with filled prescriptions of combination POA medications (i.e., oxycodone/naloxone, buprenorphine/naloxone, morphine/antispasmodics, ketobemidone/antispasmodics, hydromorphone/antispasmodics, codeine combinations, and dextropropoxyphene combinations; SIII.9 Appendix).

Fourth, to further assess whether exposure to polypharmacy was responsible for observed

associations with POA exposure, we re-estimated adjusted associations in a subsample excluding births occurring to women prescribed other psychiatric medications during pregnancy (SIII.10 Appendix).

Sibling comparison assumptions. We conducted two sets of analyses to evaluate the assumptions of sibling comparisons (SIII.11 Appendix). To evaluate whether the restriction to individuals with siblings differed from the full population, we re-estimated adjusted associations in a subsample comprised of the women that contributed more than once to the full population sample (i.e., women that had more than one singleton birth in the study period). To evaluate if the sibling comparisons were biased by carry-over effects (i.e., exposure in an earlier pregnancy affecting subsequent pregnancies), we compared differentially exposed pairs of first-born cousins.

Bias from outcome definitions. To evaluate whether any potential influence of POA exposure was not reflected in the clinical cut-off values of the birth outcomes, we fit all of the main models predicting birth outcomes on continuous scales. Specifically, we predicated (1) gestational age measured in days and (2) birth weight measured in grams adjusted for gestational age (SIII.12 Appendix).

Influence of missing data. We conducted two sensitivity analyses to evaluate whether missing data influenced our findings (SIII.13 Appendix). First, we estimated the association between absence of data and POA exposure in the target sample.

Then, we assessed the potential confounding influence of the covariates with missing by removing these covariates from the fully adjusted model in the analytic sample, and fitting this alternative model in both the analytic and target samples to evaluate whether the findings in the restricted (analytic) sample appear to represent the findings of the full (target) sample.

Results

Participants

We started with a population-based sample of 711,986 births occurring in Sweden between July, 1st 2007 and December, 31st 2013. To create the target sample, we sequentially excluded infants with invalid child identifiers (2,648), maternal identifiers (107), and sex (6); multiple births (19,844); births missing gestational age (173); and births exposed to buprenorphine or methadone for opioid use disorder treatment rather than pain (276). To create the analytic sample from the target sample, we excluded 68,474 infants with missing covariate data. The final analytic cohort of 620,458 births represented approximately 90% of the target sample. We also identified 288,995 births occurring to the same mother in the analytic sample for inclusion in sibling comparison analyses. This sample of siblings that shared mothers included 9,201 unique mothers.

Demographics

Table III.1 compares background characteristics among infants exposed to any POA during pregnancy and all the unexposed infants in the target sample. Additionally, SIII.14 Appendix shows the prevalence of background characteristics stratified by all exposure groups, including infants with single- and multiple-trimester exposure. We provided demographic data from the target sample in order to document the prevalence of missing on covariates, which ranged from none to approximately four percent.

In the final analytic sample, 4.4% of infants were exposed to POAs anytime during pregnancy with 3.7% exposed in a single trimester and 0.7% exposed in multiple trimesters (Table III.2).

Preterm birth occurred more often among exposed (6.4%) than unexposed (4.4%) infants, particularly among infants with multiple-trimester exposure (5.8% of single-trimester exposed, 9.6% of multiple-trimester exposed); and, about 2% of infants were SGA regardless of exposure status (2.1% of unexposed; 2.2% of exposed, 2.0% of single-trimester exposed, and 3.04% of multiple-trimester exposed; SIII.15 Appendix).

Associations with preterm birth

Exposure anytime during pregnancy. The unadjusted association between any exposure to POAs and PTB (odds ratio [OR]=1.48, 95% confidence interval [CI]:1.41-1.56, $p<0.001$; Table III.3) was attenuated but remained robust after adjustment for measured covariates (OR=1.38, 95% CI:1.31-1.45, $p<0.001$) and was further attenuated when we used the alternative comparison groups (comparative safety OR=1.18, 95% CI:1.07-1.30, $p<0.001$; before-pregnancy-use OR=1.05, 95% CI:0.96-1.14, $p=0.27$; siblings OR=0.99, 95% CI:0.85-1.14, $p=0.92$).

Short-term versus persistent exposure during pregnancy. We observed a similar pattern of attenuated associations with increasing confounder control also when separating single- and multiple-trimester exposure, though this also revealed that associations for multiple-trimester exposure were consistently more pronounced than for single-trimester exposure. The unadjusted associations (single-trimester OR=1.34, 95% CI:1.26-1.41, $p<0.001$ and multiple-trimester OR=2.31, 95% CI:2.08-2.55, $p<0.001$) suggested a relationship with duration of use that remained despite attenuation in adjusted models (single-trimester OR=1.27, 95% CI:1.20-1.34, $p<0.001$ and multiple-trimester OR=1.97, 95% CI:1.77-2.18, $p<0.001$); however partially attenuated when using some of the alternative comparison groups (comparative safety: single-trimester OR=0.91, 95% CI:0.83:0.99, $p=0.03$ and multiple-trimester OR=1.53, 95% CI:1.36-1.72, $p<0.001$; before-pregnancy-use: single-trimester OR=1.00, 95% CI:0.92-1.09, $p=0.99$ and

multiple-trimester OR=1.52, 95% CI:1.28-1.80, $p<0.001$) and fully attenuated in the sibling comparison (single-trimester OR=0.99, 95% CI:0.85-1.15, $p=0.87$ and multiple-trimester OR=1.04, 95% CI:0.70-1.55, $p=0.83$).

Associations with small for gestational age

Exposure anytime during pregnancy. Across models 1 through 5, associations were negligible (Table III.3).

Short-term versus persistent exposure during pregnancy. Similar to the findings for PTB, the association between POAs exposure and SGA differed according to the duration of use (Table III.3). While there was no association with single-trimester exposure (unadjusted OR=0.96, 95% CI:0.88-1.06, $p=0.43$), a moderate association with multiple-trimester exposure (unadjusted OR=1.45, 95% CI:1.22-1.73, $p<0.001$) remained in the adjusted (OR=1.40, 95% CI:1.17-1.67, $p<0.001$) and comparative safety (OR=1.41,95% CI:1.15-1.73, $p=0.001$) models but was attenuated in the before-pregnancy-use (OR=1.20, 95% CI:0.89-1.60, $p=0.23$) and siblings (OR=1.22, 95% CI:0.60-2.48, $p=0.58$) models.

Sensitivity analyses

Bias from exposure definitions. SIII.7 Appendix examined potential bias from exposure misclassification and found the same pattern of results with a number of alternative exposure definitions (i.e., the expanded prescription window definition, the restricted prescription window definition, and definition according to maternal-reported POA use or during pregnancy prescriptions). SIII.8 Appendix suggested that findings were not largely driven by, dextropropoxyphene, an opioid that is no longer prescribed, or by opioids that are also prescribed for the treatment of opioid use disorder. SIII.9 Appendix showed commensurate adjusted associations in a subsample excluding those with during-pregnancy prescriptions of combination

POA medications, suggesting that the results were not driven by inclusion of combination POA medications. Similarly, SIII.10 Appendix showed comparable adjusted associations in a subsample excluding those with during-pregnancy polypharmacy, suggesting that associations with POA exposure observed in main analyses were not driven by exposure to polypharmacy.

Sibling comparison assumptions. Two analyses in SIII.11 Appendix examined assumptions of sibling comparisons. The first analysis suggested attenuation in sibling comparisons was not due to restricting the sample to infants with siblings because population-wide associations were comparable in samples of infants with and without siblings. The second analysis suggested that sibling comparison findings were not due to carry-over effects (i.e., exposure in a prior pregnancy affecting subsequent pregnancies) because comparisons of *first-born* cousins showed the same pattern of results as the sibling comparison findings.

Bias from outcome definitions. SIII.12 Appendix demonstrated that using clinical cut-off values for the outcomes did not cause a failure to detect an influence of POA exposure by estimating associations with two continuously measured birth outcomes. Any POA exposure was associated with reduced gestational age in unadjusted models, and the associations attenuated in subsequent models. POA exposure was not associated with reduced birth weight adjusted for gestational age across any of the models.

Influence of missing data. SIII.13 Appendix suggests that excluding infants with missing data did not bias our results. Absence of data was not associated with prescriptions anytime during pregnancy after adjusting for all measured covariates in our target sample (OR=1.03, 95% CI:0.98-1.08), indicating that covariate adjustment helped minimize potential bias from missing data. Moreover, removing the covariates with missing (smoking during pregnancy; maternal and paternal education, country of origin; paternal age at childbearing; parental cohabitation status at

birth; family income; and, neighborhood deprivation) from the fully adjusted model did not meaningfully change the association in the analytic sample, and this alternative model yielded similar estimates of association in the target sample as the analytic sample.

Discussion

In a population-based sample of Swedish births occurring between 2007 and 2013, we used multiple observational designs to evaluate the consequences of prenatal POA exposure on the risk of two adverse birth outcomes – PTB and SGA. Compared with unexposed infants, infants exposed to POAs anytime during pregnancy, in a single-trimester, and in multiple trimesters were all at increased risk for PTB, though infants exposed in multiple trimesters had the greatest risk. However, when we used comparison groups consisting of unexposed infants that shared characteristics with exposed infants, the associations with PTB were attenuated, suggesting that observed associations were largely due to unmeasured confounding factors. For example, siblings exposed anytime during pregnancy, in a single trimester, and in multiple trimesters were not at increased PTB risk compared to their unexposed siblings, which suggests that unmeasured genetic and environmental factors shared by siblings account for observed population-wide associations.

For SGA, we only observed associations with persistent POA exposure (i.e. in multiple trimesters). We observed the higher risk of SGA among exposed infants when we made comparisons to unexposed infants, as well as acetaminophen-exposed infants. However, the association was attenuated when we used infants born to mothers with POA prescriptions before pregnancy only and unexposed siblings as the comparison groups, which again suggests the observed associations were largely due to confounding factors.

Our study had several noteworthy strengths that distinguish it from previous studies. First, we used multiple methods that were able to account for both measured and unmeasured sources of confounding and found converging evidence across these methods that suggested that the observed associations with birth outcomes were at least partially due to confounding. This converging evidence suggests that our conclusions are not due to violations of the assumptions of one design. Second, we reduced the potential influence from exposure misclassification by including a 90-day pre-pregnancy washout period and conducting multiple sensitivity analyses to evaluate the influence of potential exposure misclassification. Third, unlike most previous studies that examined any POA use anytime during pregnancy, we defined exposure by the number of trimesters with prescriptions and number of prescriptions throughout pregnancy, as well as evaluated for sensitive periods of exposure by estimating associations with exposure earlier and later in pregnancy. Fourth, we excluded opioids used to treat opioid use disorder. Most previous studies focused on two opioids – methadone and buprenorphine – in the context of medication assisted treatment of opioid use disorder or did not differentiate between POAs and opioids prescribed for opioid use disorder treatment. This is an important distinction because women who are prescribed opioids to manage pain presumably differ on several important background characteristics compared to women who are prescribed opioids for the treatment of opioid use disorder.

Our study also had several limitations. First, our exposure was subject to misclassification because mothers may not have taken their prescribed medications. Second, due to the rarity of the exposures, we did not evaluate associations with specific POA medications, and we did not examine pill dosages, number of pills prescribed, and number days covered. Therefore, future research should utilize finer grained measurements, such as morphine

equivalent units, which take into account number of pills prescribed, numbers of days supplied, strength per pill, and type of POA.[55] Third, the comparative safety model evaluated the relative safety of POA exposure compared to acetaminophen exposure, and a null difference could have been due to adverse effects of both medications rather than confounding by common indications for the medications. Fourth, we did not have measures of indications for POA use, although we used several methods to assess the influence of unmeasured confounding factors. Nonetheless, future research should evaluate associations with POA treatment during pregnancy among women with conditions causing chronic pain (e.g., back pain, abdominal pain, fibromyalgia, and rheumatoid arthritis)[2] in order to compare exposed to unexposed with similar conditions for which POA treatment is indicated. Fifth, we do not know if unmeasured confounding biased results. In particular, we cannot rule out the possibility that further unmeasured confounding factors account for the remaining observed associations, particularly with multiple-trimester exposure. Indeed, women who use POAs in multiple trimesters are likely to have more severe conditions requiring chronic POA treatment, which could result in greater unmeasured confounding by indication. Sixth, we do not know if our findings will generalize to countries outside of Sweden given between-country differences (e.g., higher prescribing rates in the US compared to Sweden);[2,56] however, in theory these differences would not impact the ability to detect a causal effect of POA exposure. Nonetheless, future research should evaluate whether our findings apply to populations outside of Sweden. Seventh, we excluded infants that did not have information on all covariates. However, sensitivity analyses suggested that excluding these infants from the main analyses did not influence our conclusions (SIII.13 Appendix). Eighth, we only explored two birth outcomes and were not able to explore more rare birth outcomes, such as extreme preterm birth. However, sensitivity analyses showed the same pattern of results with

continuous measures of gestational age and fetal growth (SIII.12 Appendix). Future research should examine the consequences of prenatal POA exposure on other important adverse birth outcomes (e.g., birth defects), as well as outcomes presenting later in development (e.g., autism and attention-deficit hyperactivity disorder).

Despite the limitations, our study has important clinical implications. The vast majority of infants exposed during pregnancy did not have PTB and were not SGA. The absolute risk was low even among infants with persistent exposure, with 90% not having PTB and 97% not being SGA. Although, we could not rule out small independent associations, particularly for persistent exposure during pregnancy, our results suggested that associations between prenatal POA exposure and PTB and SGA were largely due to confounding factors associated with maternal POA use during pregnancy rather than causal effects of POA exposure. We believe our findings are valuable as they may help doctors and patients better weigh the risks and benefits of POA use in women of childbearing age and pregnant women, though decision-making must consider a wide range of potential adverse outcomes. Our results also indicate that women of childbearing years should be assessed for a broad range of risk factors, and interventions aimed at reducing the incidence of adverse birth outcomes associated with maternal POA use during pregnancy should target co-occurring risk factors.

Table III.1. Demographics in the target sample

	Unexposed (n=658,580 [95.59%])	Ever Exposed (n=30,352 [4.41%])	Associations comparing exposed to unexposed	
	N (%)	N (%)	OR (95% CI)	*P*-value
Pregnancy-related characteristics				
Birth order				
1st	296455 (45.01)	11883 (39.15)	Reference	Reference
2nd	241854 (36.72)	10884 (35.86)	1.12 (1.09, 1.15)	<.001
3rd or higher	120271 (18.26)	7585 (24.99)	1.57 (1.53, 1.62)	<.001
Year of birth				
2007 to 2009	246792 (37.47)	11016 (36.29)	Reference	Reference
2010 to 2013	411788 (62.53)	19336 (63.71)	1.05 (1.03, 1.08)	<.001
Maternal smoking during the first trimester				
None	596358 (90.55)	25881 (85.27)	Reference	Reference
Moderate(1-9 cigarettes/day)	30513 (4.63)	2455 (8.09)	1.85 (1.78, 1.94)	<.001
High(≥10 cigarettes/day)	8409 (1.28)	918 (3.02)	2.52 (2.35, 2.70)	<.001
Missing	23300 (3.54)	1098 (3.62)	1.09 (1.02, 1.16)	.01
Exposure to other psychiatric medications	28432 (4.32)	4695 (15.47)	3.74 (3.63, 3.86)	<.001
Maternal characteristics				
Opioid use disorder before conception	468 (0.07)	123 (0.41)	5.72 (4.69, 6.98)	<.001
Non-opioid substance use disorder before conception	10298 (1.56)	960 (3.16)	2.06 (1.92, 2.20)	<.001
Schizophrenia or bipolar disorder before conception	2576 (0.39)	285 (0.94)	2.42 (2.14, 2.73)	<.001
Definite or uncertain suicide attempt before conception	11181 (1.70)	1247 (4.11)	2.48 (2.34, 2.63)	<.001
Any criminal convictions before conception	43190 (6.56)	3352 (11.04)	1.77 (1.70, 1.84)	<.001
Age at year of birth				
Less than 19 years	6797 (1.03)	188 (0.62)	0.62 (0.53, 0.71)	<.001
20 to 29 years	256894 (39.01)	11526 (37.97)	Reference	Reference
30 to 39 years	362436 (55.03)	16858 (55.54)	1.04 (1.01, 1.06)	<.001
40 to 45 years	31600 (4.80)	1736 (5.72)	1.22 (1.16, 1.29)	<.001
46 years and older	853 (0.13)	44 (0.14)	1.15 (0.85, 1.56)	0.37
Highest level of education at year of birth				
Less than 9 years	19895 (3.02)	865 (2.85)	Reference	Reference
9 years	50739 (7.70)	3729 (12.29)	1.69 (1.57, 1.82)	<.001
1 to 3 years upper secondary	239629 (36.39)	13022 (42.90)	1.25 (1.17, 1.34)	<.001
Any post-secondary or postgraduate	332690 (50.52)	12301 (40.53)	0.85 (0.79, 0.91)	<.001

Missing	15629 (2.37)	435 (1.43)	0.64 (0.57, 0.72)	<.001
Country of origin				
Sweden	502636 (76.32)	24079 (79.33)	1.19 (1.16, 1.23)	<.001
Missing	98 (0.01)	1 (0.00)	0.26 (0.04, 1.82)	0.17
Paternal characteristics				
Opioid use disorder before conception	984 (0.15)	102 (0.34)	2.26 (1.84, 2.77)	<.001
Non-opioid substance use disorder before conception	11554 (1.75)	832 (2.74)	1.58 (1.47, 1.70)	<.001
Schizophrenia or bipolar disorder before conception	1968 (0.30)	144 (0.47)	1.59 (1.34, 1.88)	<.001
Definite or uncertain suicide attempt before conception	7980 (1.21)	474 (1.56)	1.29 (1.18, 1.42)	<.001
Any criminal convictions before conception	120387 (18.28)	7117 (23.45)	1.37 (1.33, 1.41)	<.001
Age at year of birth				
Less than 19 years	2023 (0.31)	67 (0.22)	0.71 (0.56, 0.91)	0.01
20 to 29 years	157717 (23.95)	7352 (24.22)	Reference	Reference
30 to 39 years	377775 (57.36)	17021 (56.08)	0.97 (0.94, 0.99)	0.02
40 to 45 years	79403 (12.06)	3939 (12.98)	1.06 (1.02, 1.11)	<.001
46 years and older	27724 (4.21)	1346 (4.43)	1.04 (0.98, 1.11)	0.18
Missing	13938 (2.12)	627 (2.07)	0.97 (0.89, 1.05)	0.40
Highest level of education at year of birth				
Less than 9 years	17865 (2.71)	788 (2.60)	Reference	Reference
9 years	60313 (9.16)	3432 (11.31)	1.29 (1.19, 1.40)	<.001
1 to 3 years upper secondary	293777 (44.61)	15014 (49.47)	1.16 (1.08, 1.25)	<.001
Any post-secondary or postgraduate	259281 (39.37)	9985 (32.90)	0.87 (0.81, 0.94)	<.001
Missing	27344 (4.15)	1133 (3.73)	0.94 (0.86, 1.03)	0.19
Country of origin				
Sweden	492997 (74.86)	23367 (76.99)	1.13 (1.10, 1.16)	<.001
Missing	14042 (2.13)	629 (2.07)	1.07 (0.98, 1.16)	0.12
Other familial and socioeconomic characteristics				
Parental cohabitation status at birth				
Parents not cohabitating at birth	39845 (6.05)	2302 (7.58)	1.28 (1.22, 1.34)	<.001
Missing	24936 (3.79)	1194 (3.93)	1.06 (1.00, 1.12)	0.06
Family income at year of birth				
1st quintile (lowest income)	55036 (8.36)	2183 (7.19)	0.83 (0.79, 0.87)	<.001
2nd quintile	85747 (13.02)	4319 (14.23)	1.03 (0.99, 1.07)	0.11
3rd quintile	190101 (28.87)	9292 (30.61)	Reference	Reference
4th quintile	222018 (33.71)	10098 (33.27)	0.93 (0.90, 0.96)	<.001
5th quintile (highest income)	105678 (16.05)	4460 (14.69)	0.86 (0.83, 0.90)	<.001

Missing	2005 (0.30)	39 (0.13)	0.48 (0.35, 0.66)	<.001
Neighborhood deprivation at year of birth				
1st quintile (least)	96203 (14.61)	4179 (13.77)	0.96 (0.92, 1.00)	0.05
2nd quintile	113124 (17.18)	5037 (16.60)	0.98 (0.94, 1.02)	0.35
3rd quintile (reference)	118578 (18.01)	5379 (17.72)	Reference	Reference
4th quintile	140301 (21.30)	6532 (21.52)	1.03 (0.99, 1.07)	0.24
5th quintile (most)	190374 (28.91)	9225 (30.39)	1.07 (1.03, 1.11)	<.001
Missing	1189 (0.18)	43 (0.14)	0.83 (0.61, 1.13)	0.24

Note. OR=odds ratio. CI=confidence interval

Table III.2. Proportion of infants with prescribed opioid analgesic and acetaminophen exposure in the analytic sample

	N (%)
Prescribed opioid analgesic exposure	
Before-pregnancy-only	18883 (3.04)
Washout-period-only	7199 (1.16)
Anytime during pregnancy	27559 (4.44)
Single-trimester	23211 (3.74)
Multiple-trimesters	4348 (0.70)
Acetaminophen-only exposure	
Anytime during pregnancy	13116 (2.11)
Single-trimester	10293 (1.66)
Multiple-trimesters	2823 (0.45)

Table III.3. Associations between prescribed opioid analgesic exposure and adverse birth outcomes

	Model 1: Unadjusted		Model 2: Adjusted		Model 3: Comparative safety		Model 4: Before-pregnancy-only comparison		Model 5: Sibling comparison	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Preterm birth										
Exposure anytime during pregnancy	1.48 (1.41, 1.56)	<0.001	1.38 (1.31, 1.45)	<0.001	1.18 (1.07, 1.30)	<0.001	1.05 (0.96, 1.14)	0.27	0.99 (0.85, 1.14)	0.92
Exposure in a single trimester	1.34 (1.26, 1.41)	<0.001	1.27 (1.20, 1.34)	<0.001	0.91 (0.83, 0.99)	0.03	1.00 (0.92, 1.09)	0.99	0.99 (0.85, 1.15)	0.87
Exposure in multiple trimesters	2.31 (2.08, 2.55)	<0.001	1.97 (1.77, 2.18)	<0.001	1.53 (1.36, 1.72)	<0.001	1.52 (1.28, 1.80)	<0.001	1.04 (0.70, 1.55)	0.83
Small for gestational age										
Exposure anytime during pregnancy	1.04 (0.96, 1.13)	0.35	1.02 (0.93, 1.10)	0.64	0.98 (0.85, 1.13)	0.80	0.93 (0.81, 1.06)	0.26	0.91 (0.70, 1.19)	0.55
Exposure in a single trimester	0.96 (0.88, 1.06)	0.43	0.95 (0.87, 1.04)	0.29	0.87 (0.76, 1.01)	0.06	0.90 (0.78, 1.03)	0.13	0.90 (0.69, 1.18)	0.44
Exposure in multiple trimesters	1.45 (1.22, 1.73)	<0.001	1.40 (1.17, 1.67)	<0.001	1.41 (1.15, 1.73)	0.001	1.20 (0.89, 1.60)	0.23	1.22 (0.60, 2.48)	0.58

Note. OR=odds ratio. CI=confidence interval. Models 1 and 2 estimated population-wide associations with POA-exposed infants compared to unexposed infants. Model 1 did not include any covariates. Model 2 included all measured characteristics as covariates in the regression models. Models 3 through 5 used alternative comparison groups consisting of infants likely to share some characteristics with exposed infants while also controlling for measured covariates. Model 3 compared infants born to women prescribed POAs during pregnancy to infants born to women prescribed acetaminophen only during pregnancy. Model 4 compared infants born to women prescribed POAs during pregnancy to infants born to women prescribed POA before but not during pregnancy. Model 5 compared POA-exposed infants to their unexposed siblings.

References

1. Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. *Obstet Gynecol.* 2014;123(5):997-1002.
2. Bateman BT, Hernandez-Diaz S, Rathmell JP, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. *Anesthesiology.* 2014;120(5):1216-1224.
3. Kroll-Desrosiers AR, Skanderson M, Bastian LA, et al. Receipt of Prescription Opioids in a National Sample of Pregnant Veterans Receiving Veterans Health Administration Care. *Womens Health Issues.* 2016;26(2):240-246.
4. Engeland A, Bramness JG, Daltveit AK, Ronning M, Skurtveit S, Furu K. Prescription drug use among fathers and mothers before and during pregnancy. A population-based cohort study of 106,000 pregnancies in Norway 2004-2006. *Br J Clin Pharmacol.* 2008;65(5):653-660.
5. Epstein RA, Bobo WV, Martin PR, et al. Increasing pregnancy-related use of prescribed opioid analgesics. *Annals of Epidemiology.* 2013;23(8):498-503.
6. Malek A, Mattison DR. Drugs and Medicines in Pregnancy: The Placental Disposition of Opioids. *Current Pharmaceutical Biotechnology.* 2011;12(5):797-803.
7. Lind JN, Interrante JD, Ailes EC, et al. Maternal Use of Opioids During Pregnancy and Congenital Malformations: A Systematic Review. *Pediatrics.* 2017;139(6).
8. Yazdy MM, Desai RJ, Brogly SB. Prescription Opioids in Pregnancy and Birth Outcomes: A Review of the Literature. *J Pediatr Genet.* 2015;4(2):56-70.

9. Brennan MC, Rayburn WF. Counseling about risks of congenital anomalies from prescription opioids. *Birth Defects Res A Clin Mol Teratol.* 2012;94(8):620-625.

10. Disher T, Gullickson C, Singh B, et al. Pharmacological Treatments for Neonatal Abstinence Syndrome: A Systematic Review and Network Meta-analysisPharmacological Treatments for Neonatal Abstinence SyndromePharmacological Treatments for Neonatal Abstinence Syndrome. *JAMA Pediatrics.* 2019;173(3):234-243.

11. Reddy UM, Davis JM, Ren Z, Greene MF. Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes: Executive Summary of a Joint Workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. *Obstet Gynecol.* 2017;130(1):10-28.

12. Wachman EM, Schiff DM, Silverstein M. Neonatal Abstinence Syndrome Advances in Diagnosis and Treatment. *JAMA-J Am Med Assoc.* 2018;319(13):1362-1374.

13. Brogly SB, Saia KA, Walley AY, Du HM, Sebastiani P. Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis. *Am J Epidemiol.* 2014;180(7):673-686.

14. Grossman M, Seashore C, Holmes AV. Neonatal Abstinence Syndrome Management: A Review of Recent Evidence. *Rev Recent Clin Trials.* 2017;12(4):226-232.

15. Creanga AA, Berg CJ, Ko JY, et al. Maternal Mortality and Morbidity in the United States: Where Are We Now? *Journal of Women's Health.* 2014;23(1):3-9.

16. Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics.* 2015;135(5):842-850.

17. Class QA, Rickert ME, Langstrom N, Lichtenstein P, D'Onofrio BM. Birth weight, physical morbidity, and mortality: A population-based sibling-comparison study. *American Journal of Epidemiology.* 2014;179:550-558.

18. Class QA, Rickert ME, Larsson H, Lichtenstein P, D'Onofrio BM. Fetal growth and psychiatric and socioeconomic problems: population-based sibling comparison *British Journal of Psychiatry.* 2014;205(5):355-361.

19. D'Onofrio BM, Class QA, Rickert ME, Larsson H, Langstrom N, Lichtenstein P. Preterm birth and mortality and morbidity: A population-based quasi-experimental study. *JAMA Psychiatry.* 2013;70:1231-1240.

20. Quinn PD, Hur K, Chang Z, et al. Incident and long-term opioid therapy among patients with psychiatric conditions and medications: A national study of commercial health care claims. *Pain.* 2017;158(1):140-148.

21. Gustavsson A, Bjorkman J, Ljungcrantz C, et al. Pharmaceutical treatment patterns for patients with a diagnosis related to chronic pain initiating a slow-release strong opioid treatment in Sweden. *Pain.* 2012;153(12):2325-2331.

22. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: Retrospective analysis. *BMJ.* 2017;356:j760.

23. Fredheim OMS, Borchgrevink PC, Mahic M, Skurtveit S. A pharmacoepidemiological cohort study of subjects starting strong opioids for nonmalignant pain: A study from the Norwegian Prescription Database. *Pain.* 2013;154(11):2487-2493.

24. Larochelle MR, Zhang F, Ross-Degnan D, Wharam JF. Trends in opioid prescribing and co-prescribing of sedative hypnotics for acute and chronic musculoskeletal pain: 2001–2010. *Pharmacoepidemiology and Drug Safety.* 2015;24(8):885-892.

25. Kobus AM, Smith DH, Morasco BJ, et al. Correlates of higher-dose opioid medication use for low back pain in primary care. *Journal of Pain.* 2012;13(11):1131-1138.

26. Morales DR, Slattery J, Evans S, Kurz X. Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: systematic review of observational studies and methodological considerations. *BMC Medicine.* 2018;16(1):6.

27. Pourhoseingholi MA, Baghestani AR, Vahedi M. How to control confounding effects by statistical analysis. *Gastroenterology and Hepatology From Bed to Bench.* 2012;5(2):79-83.

28. Rutter M. Psychosocial influences: Critiques, findings, and research needs. *Development and Psychopathology.* 2000;12:375-405.

29. Academy of Medical Sciences Working Group. *Identifying the environmental causes of disease: How should we decide what to believe and when to take action?* London: Academy of Medical Sciences; 2007.

30. Shadish WR, Cook TD, Campbell DT. *Experimental and quasi-experimental designs for generalized causal inference.* New York: Houghton Mifflin; 2002.

31. Statistics Sweden. https://www.scb.se/en/.

32. Statistics Sweden. *Multi-Generation Register 2009 - A Description of Contents and Quality.* Örebro, Sweden2010.

33. National Board of Health and Welfare. *4 years with the Prescribed Drug Register [in Swedish].* Stockholm: National Board of Health and Welfare;2010.

34. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiology and drug safety.* 2007;16(7):726-735.

35. National Board of Health and Welfare. *The Swedish Medical Birth Register - A Summary of Content and Quality.* Stockholm: National Board of Health and Welfare;2003.

36. Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. *Scand J Soc Med.* 1990;18(2):143-148.

37. National Board of Health and Welfare. *Pregnancies, Deliveries and Newborn Infants - The Swedish Medical Birth Register 1973-2011, Assisted Reproduction, treatment 1991-2010 [in Swedish].* Stockholm2013.

38. National Board of Health and Welfare. *Quality and Content in the Patient Register - Inpatient care discharges 1964-2007 and outpatient (specialized care) visits 1997-2007 [in Swedish].* Stockholm: National Board of Health and Welfare;2009. 2009-125-15.

39. WHO. *International Classification of Diseases, World Health Organization WHO.* Geneva1992.

40. BRÅ e. Kriminalstatistik 2010 [Criminal statistics]. . In: Västerås, ed2011.

41. Fazel S, Grann M. The population impact of severe mental illness on violent crime. *American Journal of Psychiatry.* 2006;163(8):1397-1403.

42. Statistics Sweden. Education in Sweden 2009. http://www.scb.se/statistik/_publikationer/uf0527_2009a01_br_uf08br0901.pdf. Published 2009. Updated February 21, 2014. Accessed.

43. LISA database. http://www.scb.se/Pages/List____257743.aspx. Accessed.

44. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC classification and DDD assignment 2014.* Oslo: Author;2013.

45. Abrahamsson T, Berge J, Ojehagen A, Hakansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment-A nation-wide register-based open cohort study. *Drug Alcohol Depend.* 2017;174:58-64.

46. Hampp C, Gelperin K, Taylor L, et al. Misclassification in Assessment of First Trimester In-utero Exposure to Drugs Used Proximally to Conception: the Example of Letrozole Utilization for Infertility Treatment. *American Journal of Epidemiology.* 2018;188(2):418-425.

47. Hagenfeldt K, Alton V, Axelsson O, et al. Routine ultrasound examination during pregnancy - summary in English. Stockholm: The Swedish Council on Health Technology Assessment (SBU). 1998.

48. Soderberg KC, Laflamme L, Moller J. Newly initiated opioid treatment and the risk of fall-related injuries. A nationwide, register-based, case-crossover study in Sweden. *Cns Drugs.* 2013;27(2):155-161.

49. Quinn PD, Rickert ME, Franck J, et al. Associations of mental health and family background with opioid analgesic therapy: a nationwide Swedish register-based study. *Pain.* 2019.

50. Sariaslan A, Langstrom N, D'Onofrio B, Hallqvist J, Franck J, Lichtenstein P. The impact of neighbourhood deprivation on adolescent violent criminality and substance misuse: a longitudinal, quasi-experimental study of the total Swedish population. *Int J Epidemiol.* 2013;42(4):1057-1066.

51. Pearl J. *Causality: Models, Reasoning and Inference.* Cambridge: Cambridge University Press; 2000.

52. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: Historical foundations and contemporary application. *Current Epidemiology Reports.* 2015;2(4):221-228.

53. Smith GD. Assessing intrauterine influences on offspring health outcomes: can epidemiological studies yield robust findings? *Basic Clin Pharmacol Toxicol.* 2008;102(2):245-256.

54. D'Onofrio BM, Class QA, Rickert ME, et al. Translational Epidemiologic Approaches to Understanding the Consequences of Early-Life Exposures. *Behav Genet.* 2016;46(3):315-328.

55. Svendsen K, Borchgrevink PC, Fredheim O, Hamunen K, Mellbye A, Dale O. Choosing the unit of measurement counts: The use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. *Palliative Medicine.* 2011;25(7):725-732.

56. Handal M, Engeland A, Ronning M, Skurtveit S, Furu K. Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: a population-based cohort study. *European Journal of Clinical Pharmacology.* 2011;67(9):953-960.

SIII.1 Appendix: STROBE Checklist

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Section
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract – Methods/findings
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract – Methods/findings & Results subsections
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction – Paragraphs 1 & 2
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction – Paragraph 2
Methods			
Study design	4	Present key elements of study design early in the paper	Methods – Paragraph 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods – Paragraph 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods – Paragraph 1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods – Measures subsection
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods – Measures subsection
Bias	9	Describe any efforts to address potential sources of bias	Methods – Associations between POA exposure and birth outcomes subsection
Study size	10	Explain how the study size was arrived at	Methods – Paragraph 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods – Associations between POA exposure and birth outcomes subsection
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods – Associations between POA exposure and birth outcomes subsection
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	Methods – Paragraph 1
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	Methods –Sensitivity analyses subsection
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results – Participants subsection
		(b) Give reasons for non-participation at each stage	Results – Participants subsection
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results – Demographics subsection, Table III.1
		(b) Indicate number of participants with missing data for each variable of interest	Results – Demographics subsection, Table III.1
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results – Demographics subsection, SIII.14 Appendix
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results -- Associations with preterm birth subsection, Associations with small for gestational age subsection, Table III.3
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results – Demographics subsection, SIII.14 Appendix
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results – Sensitivity analyses subsection, SIII.6 to SIII.12 Appendixes
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion – Paragraphs 1 & 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion – Paragraph 4
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion – Paragraph 5
Generalizability	21	Discuss the generalisability (external validity) of the study results	Discussion – Paragraph 4
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgements

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

SIII.2 Appendix: Planned analyses

While we did not register a formal pre-specified analyses plan prior to conducting this study, the analyses presented in the paper were pre-planned, with the exception of several exploratory sensitivity analyses that we added to respond to feedback we received at conferences and during the review process. Prior to conducting this study, we described our planned approach in several grant submissions, including grants that have been funded by the National Institute on Drug Abuse and the Swedish Research Counsel. The current paper is the first paper among many that we described in the grants. For the current paper, we also followed a similar analytic strategy as the one we used in our paper on antidepressant use during pregnancy that was published in *JAMA* in 2017.[1] Below, we have summarized our plan and where we deviated from our plans outlined in the grant proposals.

Hypotheses: In the grant proposals, we hypothesized:

(a) Maternal prescribed opioid analgesic (POA) use in pregnancy would be more common among women with psychiatric comorbidities, socioeconomic risk, and co-occurring pregnancy exposures and that

(b) POA use in pregnancy would be associated with increased risk of adverse offspring outcome also after adjustment for these and unmeasured potential sources of confounding, consistent with true adverse effects.

Sample: In the grants, we proposed analyzing a dataset created by linking several Swedish population registers, which we analyzed in our 2017 JAMA paper.[1] The grants also proposed analyzing a dataset with additional years, but this dataset is not available yet.

Exposures: In the grants, we outlined how we would use several indicators of POA exposure. We described how we would focus on any POA use during pregnancy, as well as the timing of

exposure during pregnancy. We also explained that we would eventually utilize more fine-grained exposures, and plan to do so in future studies.

Background characteristics: In the grants, we described how we could select and adjust for measured traits that may confound associations between POA exposure and offspring outcomes. These traits included several pregnancy, maternal, paternal, familial, and neighborhood characteristics. We selected the same covariates as in our JAMA 2017 paper[1] plus some additional traits that would help us better index plausible confounding factors. The additional traits, which we specified in the grant proposals, were smoking during pregnancy, exposure to other psychiatric medication during pregnancy, parental substance use disorder diagnoses, parental cohabitation status at birth, neighborhood income, and neighborhood deprivation.

Outcomes: In the grants, we proposed studying associations with preterm birth, small for gestational age, and several other outcomes. We did not include the other outcomes in this paper because we are waiting for a larger dataset that includes offspring born through 2017.

Main analyses to evaluate associations: In the grants, we outlined five approaches for estimating the risk associated with prenatal POA exposure for each offspring outcome. We had previously used four out of the five of these approaches to study associations with antidepressant use during pregnancy.[1]

First, we proposed ***adjusting for measured background factors*** that we found to be associated with POA use during pregnancy. Second, we described how we could use ***sibling comparisons*** to account for all unmeasured genetic and environmental factors that make siblings similar, including all maternal characteristics that remain stable across pregnancies. Third, we explained how we could use an ***active comparator*** medication, such as acetaminophen, to account for all unmeasured confounding factors that are common to the use of both types of

medication, including shared indications for use. Fourth, we proposed a ***timing of exposure comparison*** in which we would compare offspring of women who filled POA prescriptions during pregnancy to offspring of women who filled POA prescriptions before pregnancy only to account for confounding by all factors shared by women with POA prescriptions around the time of pregnancy, such as having a condition for which treatment is indicated. Fifth, we proposed using ***paternal POA use in pregnancy as a negative control*** to further test the role of familial confounding. We ultimately decided not to include the paternal comparison because we now believe that several of the assumptions required in the design are not met when studying maternal POA use.[e.g., 2]

Sensitivity analyses: We have written extensively about the assumptions of the designs we planned to use in this project [e.g., 3] and have developed several approaches to explore key limitations.[e.g., 1] Thus, the majority of the sensitivity analyses were pre-planned. However, in response to a concerns raised when presenting preliminary analyses at the Behavior Genetics Conference in June 2018, we added a sensitivity analyses evaluating the influence of exposure to medications included in combination POA medications (SIII.9 Appendix); and, in response to reviewers' concerns about our choice to conduct a complete-case analysis, we added a series of sensitivity analyses evaluating the role of missing data (SIII.13 Appendix). In our grants, we also proposed to evaluate the influence of carry-over effects in sibling comparison models using case-crossover analyses; however, we decided against this approach due to confounding by maternal age and calendar time and instead tested for carry-over effects by using first-born cousin comparisons. Additionally, in the grants, we proposed conducting further sensitivity analyses to test for misclassification, which we plan to do in future studies.

References

1. Sujan, A. C., Rickert, M. E., Oberg, et al. (2017). 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, 317*(15), 1553-1562.
2. Sanderson, E., MacDonald-Wallis, C., Smith, G.D. (2018). Negative control exposure studies in the presence of measurement error: Implications for attempted effect estimate calibration. *International Journal of Epidemiology, 47*(2), 587-596.
3. D'Onofrio BM, Class QA, Rickert ME, et al. (2016) Translational Epidemiologic Approaches to Understanding the Consequences of Early-Life Exposures. *Behavior Genetics, 46*(3), 315-328.

SIII.3 Appendix: Additional information on medication exposures

Prescribed opioid analgesic medications

In order to provide information on the specific POAs included in the study, sTable III.1 provides the proportions of specific types of POA medications among all POA prescriptions received by mothers during the pregnancy period. For example, of the 51,596 POA filled prescriptions filled by pregnant women between July 1st 2007 and December 31st 2013, 30,968 (60.05%) were codeine combinations.

In order to illustrate the types of clinics that prescribe POAs in Sweden, sTable III.2 provides the proportion of POA prescriptions prescribed by specific types of clinics among all POA prescriptions received by mothers during the pregnancy period in the year 2013. For example, of the 8,048 prescriptions filled by pregnant women in 2013, 2,698 (33.52%) originated from obstetrics and gynecology clinics, and 2,489 (30.93%) originated from primary care clinics.

In order to provide clarity on how we created the different POA exposures, sFigure III.1 illustrates the main windows for filled prescriptions we used to define use (a) before pregnancy, (b) in the washout period, (c) anytime during pregnancy, and (c) in the first trimester of pregnancy, (d) in the second trimester of pregnancy, and (e) in the third trimester of pregnancy.

Other medications

We included exposure to other psychiatric medication during pregnancy as a covariate in some analyses. sTable III.3 includes anatomical therapeutic chemical codes for the classes of medications we included.

sTable III.1. Type of prescribed opioid analgesic medications received by mothers during the pregnancy period

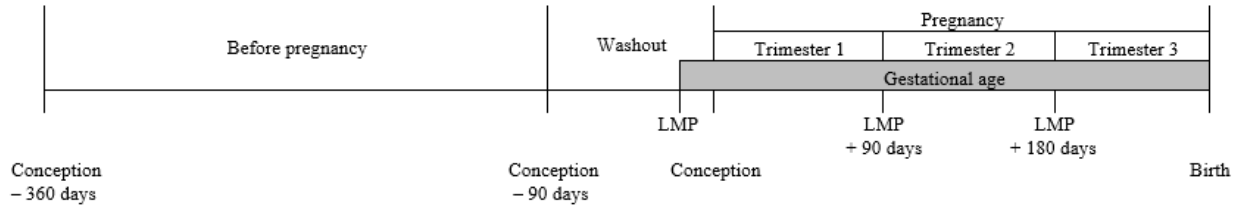
Type of prescribed opioid analgesic	Anatomical Therapeutic Chemical Codes	Maternal filled prescriptions
		N (%)
Morphine	N02AA01	592 (1.15)
Hydromorphone	N02AA03	3 (0.01)
Oxycodone	N02AA05	900 (1.75)
Oxycodone/naloxone	N02AA55	16 (0.03)
Codeine/acetaminophen	N02AA59	30968 (60.05)
Ketobemidone	N02AB01	212 (0.41)
Fentanyl	N02AB03	170 (0.33)
Dextropropoxyphene	N02AC04	10785 (20.91)
Buprenorphine	N02AE01	210 (0.41)
Morphine/antispasmodics	N02AG01	2948 (5.71)
Ketobemidone/antispasmodics	N02AG02	121 (0.23)
Tramadol	N02AX02	4531 (8.78)
Tapentadol	N02AX06	4 (0.01)
Acetaminophen/codeine	NO2BE51	24 (0.05)
Buprenorphine	N07BC01	37 (0.07)
Methadone	N07BC02	75 (0.15)
Buprenorphine, combinations	N07BC51	0 (0.00)
Total		51596 (100.00)

sTable III.2. Types of clinics prescribing opioid analgesic medications received by mothers during the pregnancy period in 2013

	Maternal filled prescriptions
Clinic type	**N (%)**
Obstetrics and gynecology	2699 (33.51)
Primary care	2493 (30.95)
Maternity care	1134 (14.08)
Surgery	345 (4.28)
Non-surgical orthopedics	230 (2.86)
Emergency	201(2.50)
Internal medicine	171 (2.12)
Anesthesiology	109 (1.35)
Non-surgical dental	109 (1.35)
Neurology	70 (0.87)
Gastrointestinal	53 (0.66)
Psychiatry	50 (0.62)
Other	341 (4.23)
Missing	50 (0.62)
Total	8055 (100.00)

sTable III.3. Other psychiatric medication classes

Medication Classes	Anatomical Therapeutic Chemical Codes
Antidepressants	N06A
Benzodiazepines	N05BA, N05CD, N05CF, N03AE01
Non-benzodiazepine anxiolytics	N05BB, N05BC, N05BD, N05BE, N05BX
Non-benzodiazepine hypnotics and sedatives	N05CA, N05CB, N05CC, N05CE, N05CH, N05CM, N05CX
Mood stabilizers and anticonvulsants	N03A, N05AN01
Antipsychotics	N05A (excluding N05AN01)
Attention-deficit/hyperactivity disorder medications	N06BA01, N06BA02, N06BA04, N06BA09
Substance use disorder medications	N07BA (excluding N07BA02) N07BB



sFigure III.1. Exposure windows. Last menstrual period (LMP) defined as birth date minus gestational age. Conception defined as LMP plus 14 days. Trimesters defined according to LMP due to the clinical practice of dating pregnancy from LMP with trimester 1 defined as conception to 89 days after LMP, trimester 2 defined as 90 to 179 days after LMP, and trimester 3 defined as 180 days after LMP to birth.

SIII.4 Appendix: Preliminary analyses exploring for sensitive periods of exposure

In order to evaluate whether there are sensitive periods of exposure during pregnancy, we assessed adjusted associations with maternal POA filled prescriptions occurring in only the first-trimester (conception to 89 days after last menstrual period) and only the second- or third-trimester (90 days after last menstrual to birth). We conducted Wald χ^2 tests to evaluate if these associations were statistically significantly different. Because these analyses intended to evaluate exposure during specific periods, we included incident users (i.e., no filled POA prescriptions in the period 360 days before pregnancy to conception) and excluded infants exposed to more than one POA during pregnancy.

In this sample of 583,686 infants born to incident users, 2,960 (0.51%) were born to women who filled a prescription only in the first trimester and 13,909 (2.38%) were born to women who filled a prescription only in the second or third trimester. The magnitude of the associations with first-trimester exposure only were slightly larger than the magnitude of associations with second/third-trimester exposure (sTable III.4); however, the associations were not statistically significantly different for both PTB (p=0.25) and SGA (p=0.54). Therefore, these results suggest that there may not be sensitive periods of exposure during pregnancy.

sTable III.4. Adjusted associations with exposure in the first trimester only and in the second/third trimester only in a subsample of incident users

	1st trimester only	**2nd/3rd trimester only**
	OR (95% CI)	**OR (95% CI)**
Preterm birth	1.32 (1.13, 1.53)	1.19 (1.10, 1.28)
Small for gestation age	1.00 (0.78, 1.23)	0.91 (0.81, 1.03)

Note. OR=odds ratio. CI=confidence interval.

SIII.5 Appendix. Review of models used to evaluate associations between prescribed opioid analgesic use and birth outcomes

In order to provide clarity on how we set up the models, sTable III.5 describes the sample used, the main predictor(s) and covariates included, and the comparison group for each main analyses model.

sTable III.5. Main models assessing associations with prescribed opioid analgesics

Models assessing associations with prescribed opioid analgesics anytime during pregnancy				
Model	**Sample**	**Main predictor**	**Other covariates**	**Comparison group**
Model 1: Unadjusted	Whole analytic sample	1. Maternal POAs anytime during pregnancy	1. Maternal POAs in washout period but not pregnancy	No maternal POAs in the washout period or pregnancy
Model 2: Adjusted	Whole analytic sample	1. Maternal POAs anytime during pregnancy	1. Maternal POAs in washout period but not pregnancy 2. Pregnancy-related, familial, and socio-economic characteristics	No maternal POAs in the washout period or pregnancy
Model 3: Comparative safety	Infants with maternal POAs and/or pure acetaminophen anytime during pregnancy	1. Maternal POAs anytime during pregnancy	1. Maternal POAs in washout period but not pregnancy 2. Pregnancy-related, familial, and socio-economic characteristics	Maternal pure acetaminophen anytime during pregnancy and no POAs in the washout period or pregnancy
Model 4: Before-pregnancy-only comparison	Infants with maternal POAs sometime in the period 360 days before conception to birth. Excluded infants with POAs both before and during pregnancy.	1. Maternal POAs anytime during pregnancy and no maternal POAs before pregnancy	1. Maternal POAs in washout period but not pregnancy 2. Pregnancy-related, familial, and socio-economic characteristics	Maternal POAs before but not in the washout period or pregnancy
Model 5: Sibling comparison	Siblings that differed on POA exposure or at least one covariate.	1. Maternal POAs anytime during pregnancy	1. Maternal POAs in washout period but not pregnancy 2. Pregnancy-related, familial, and socio-economic characteristics	Siblings with no maternal POAs in the washout period or pregnancy
Models assessing associations with prescribed opioid analgesics in a single trimester and in multiple trimesters				
Model 1: Unadjusted	Whole analytic sample	1. Maternal POAs in a single trimester 2. Maternal POAs in multiple trimesters	1. Maternal POAs in washout period but not pregnancy	No maternal POAs in the washout period or pregnancy
Model 2: Adjusted	Whole analytic sample	1. Maternal POAs in a single trimester 2. Maternal POAs in multiple trimesters	1. Maternal POAs in washout period but not pregnancy 2. Pregnancy-related, familial, and socio-economic characteristics	No maternal POAs in the washout period or pregnancy

Model 3a: Comparative safety model	Infants with maternal POAs and/or pure acetaminophen in a single trimester	1. Maternal POAs in a single trimester	1. Maternal POAs in washout period but not pregnancy 2. Pregnancy-related, familial, and socio-economic characteristics	Maternal pure acetaminophen in a single trimester and no POAs in the washout period or pregnancy
Model 3b: Comparative safety model	Infants with maternal POAs and/or pure acetaminophen in multiple trimesters	1. Maternal POAs multiple trimesters	1. Maternal POAs in washout period but not pregnancy 2. Pregnancy-related, familial, and socio-economic characteristics	Maternal pure acetaminophen in multiple trimesters and no POAs in the washout period or pregnancy
Model 4: Before-pregnancy-only comparison	Infants with maternal POAs sometime in the period 360 days before conception to birth. Excluded infants with POAs both before and during pregnancy.	1. Maternal POAs in a single trimester but not before pregnancy 2. Maternal POAs in multiple trimesters but not before pregnancy	1. Maternal POAs in washout period but not pregnancy 2. Pregnancy-related, familial, and socio-economic characteristics	Maternal POAs before pregnancy but not in the washout period or pregnancy
Model 5: Sibling comparison	Siblings that differed on POA exposure or at least one covariate.	1. Maternal POAs in a single trimester 2. Maternal POAs in multiple trimesters	1. Maternal POAs in washout period but not pregnancy 2. Pregnancy-related, familial, and socio-economic characteristics	Siblings with no maternal POAs in the washout period or pregnancy

Note. POA=prescribed opioid analgesic

SIII.6 Appendix: All parameter estimates from adjusted models estimating associations with maternal prescribed opioid filled prescriptions anytime during pregnancy

In order to be transparent and comprehensive, we provide parameter estimates and confidence intervals for all predictors included in the adjusted models predicting PTB (sTable III.6) and SGA (sTable III.7) from POA use anytime during pregnancy.

sTable III.6. Associations with preterm birth

	OR (95% CI)
Maternal prescribed opioid analgesics	
During pregnancy	1.38 (1.31, 1.45)
During the washout period only	1.24 (1.12, 1.37)
Pregnancy-related characteristics	
Birth order (reference: 1st)	
2nd	0.60 (0.58, 0.62)
3rd or higher	0.68 (0.66, 0.71)
Year of birth 2010 to 2013 (reference: 2007 to 2009)	0.97 (0.94, 0.99)
Maternal smoking during the first trimester (reference: none)	
Moderate (1 to 9 cigarettes per day)	1.21 (1.14, 1.27)
High (10 or more cigarettes per day)	1.50 (1.38, 1.64)
Exposure to other psychiatric medications	1.50 (1.43, 1.57)
Maternal characteristics	
Opioid use disorder prior to conception	0.89 (0.62, 1.28)
Non-opioid substance use disorder prior to conception	1.00 (0.91, 1.09)
Schizophrenia or bipolar disorder prior to conception	0.96 (0.81, 1.14)
Definite or uncertain suicide attempt prior to conception	1.06 (0.97, 1.15)
Any criminal convictions prior to conception	1.01 (0.96, 1.06)
Age at year of birth (reference: 20 to 29 years)	
Less than 19 years	0.98 (0.85, 1.11)
30 to 39 years	1.11 (1.08, 1.15)
40 to 45 years	1.46 (1.37, 1.55)
46 years and older	1.48 (1.08, 2.01)
Highest level of education at year of birth (reference: less than 9 years)	
9 years	1.07 (0.98, 1.17)
1 to 3 years upper secondary	1.01 (0.93, 1.09)
Any post-secondary or postgraduate	0.91 (0.84, 0.98)
Swedish nationality	0.91 (0.87, 0.94)
Paternal characteristics	
Opioid use disorder prior to conception	1.03 (0.79, 1.35)
Non-opioid substance use disorder prior to conception	0.95 (0.87, 1.04)
Schizophrenia or bipolar disorder prior to conception	1.08 (0.89, 1.31)
Definite or uncertain suicide attempt prior to conception	1.02 (0.92, 1.13)
Any criminal convictions prior to conception	1.04 (1.01, 1.07)
Age at year of birth (reference: 20 to 29 years)	
Less than 19 years	1.00 (0.80, 1.25)
30 to 39 years	0.98 (0.94, 1.01)
40 to 45 years	1.01 (0.96, 1.06)
46 years and older	1.07 (1.00, 1.14)
Highest level of education at year of birth (reference: less than 9 years)	
9 years	0.99 (0.91, 1.08)
1 to 3 years upper secondary	1.01 (0.93, 1.09)
Any post-secondary or postgraduate	0.92 (0.84, 1.00)
Swedish nationality	1.18 (1.14, 1.23)
Other familial and socioeconomic characteristics	
Parents not cohabitating at birth	0.98 (0.93, 1.04)
Family income at year of birth (reference: 3rd quintile)	
1st quintile	1.06 (1.01, 1.12)
2nd quintile	1.05 (1.01, 1.09)
4th quintile	1.01 (0.98, 1.04)
5th quintile	0.94 (0.90, 0.98)
Neighborhood deprivation at year of birth (reference: 3rd quintile)	
1st quintile	1.00 (0.96, 1.05)

2nd quintile	1.03 (0.98, 1.07)
4th quintile	1.02 (0.98, 1.06)
5th quintile	1.05 (1.01, 1.09)

Note. OR=odds ratio. CI=confidence interval.

sTable III.7. Associations with small for gestational age

	OR (95% CI)
Maternal prescribed opioid analgesics	
During pregnancy	1.02 (0.93, 1.10)
During the washout period only	1.00 (0.86, 1.17)
Pregnancy-related characteristics	
Birth order (reference: 1st)	
2nd	0.39 (0.37, 0.41)
3rd or higher	0.36 (0.34, 0.38)
Year of birth 2010 to 2013 (reference: 2007 to 2009)	0.97 (0.93, 1.00)
Maternal smoking during the first trimester (reference: none)	
Moderate (1 to 9 cigarettes per day)	2.02 (1.90, 2.16)
High (10 or more cigarettes per day)	2.77 (2.50, 3.07)
Exposure to other psychiatric medications	1.09 (1.01, 1.18)
Maternal characteristics	
Opioid use disorder prior to conception	0.91 (0.56, 1.48)
Non-opioid substance use disorder prior to conception	0.97 (0.85, 1.11)
Schizophrenia or bipolar disorder prior to conception	0.85 (0.66, 1.10)
Definite or uncertain suicide attempt prior to conception	0.90 (0.79, 1.02)
Any criminal convictions prior to conception	0.95 (0.89, 1.02)
Age at year of birth (reference: 20 to 29 years)	
Less than 19 years	0.64 (0.53, 0.78)
30 to 39 years	1.30 (1.24, 1.36)
40 to 45 years	1.72 (1.57, 1.88)
46 years and older	1.68 (1.08, 2.62)
Highest level of education at year of birth (reference: less than 9 years)	
9 years	0.92 (0.83, 1.02)
1 to 3 years upper secondary	0.81 (0.74, 0.89)
Any post-secondary or postgraduate	0.73 (0.67, 0.81)
Swedish nationality	0.75 (0.71, 0.79)
Paternal characteristics	
Opioid use disorder prior to conception	1.24 (0.88, 1.73)
Non-opioid substance use disorder prior to conception	0.90 (0.79, 1.02)
Schizophrenia or bipolar disorder prior to conception	0.96 (0.72, 1.26)
Definite or uncertain suicide attempt prior to conception	1.05 (0.91, 1.21)
Any criminal convictions prior to conception	0.98 (0.93, 1.02)
Age at year of birth (reference: 20 to 29 years)	
Less than 19 years	1.19 (0.89, 1.58)
30 to 39 years	1.12 (1.07, 1.18)
40 to 45 years	1.24 (1.16, 1.33)
46 years and older	1.28 (1.16, 1.40)
Highest level of education at year of birth (reference: less than 9 years)	
9 years	0.80 (0.73, 0.89)
1 to 3 years upper secondary	0.75 (0.69, 0.83)
Any post-secondary or postgraduate	0.73 (0.66, 0.80)
Swedish nationality	0.85 (0.80, 0.89)
Other familial and socioeconomic characteristics	
Parents not cohabitating at birth	1.11 (1.03, 1.19)
Family income at year of birth (reference: 3rd quintile)	
1st quintile	1.24 (1.15, 1.32)
2nd quintile	1.16 (1.06, 1.18)
4th quintile	0.93 (0.88, 0.97)
5th quintile	0.83 (0.78, 0.88)
Neighborhood deprivation at year of birth (reference: 3rd quintile)	
1st quintile	1.00 (0.93, 1.07)

2nd quintile	1.01 (0.95, 1.08)
4th quintile	1.01 (0.96, 1.07)
5th quintile	1.11 (1.05, 1.17)

Note. OR=od

SIII.7 Appendix: Sensitivity analyses evaluating for potential bias from exposure misclassification

In order to evaluate for potential bias from exposure misclassification, we re-estimated the adjusted associations using a number of alternative exposure definitions.

First, we expanded the exposure window to include POA prescriptions filled in the 90 days prior to conception in case a prescription that was filled shortly before pregnancy was used during pregnancy. According to this definition, 34,758 (5.60%) infants were exposed anytime during pregnancy, 29,362 (4.73%) infants were exposed in a single trimester, and 5,396 (0.87%) were exposed in multiple trimesters.

Second, we restricted the exposure window to exclude prescriptions filled in the three days before birth to exclude prescriptions that may have been filled shortly before delivery but used only after delivery. According to this definition, 27,183 (4.38%) infants were exposed anytime during pregnancy, 22,835 (3.68%) infants were exposed in a single trimester, and 4,348 (0.70%) were exposed in multiple trimesters.

Third, in order to capture some women who may have filled POA prescription before pregnancy but used them during pregnancy, we expanded our main exposure definition to include infants with maternal-reported POA use (i.e., we defined exposure according to filled prescriptions or maternal-reported use). The Medical Birth Register contains information on maternal reports of medication use at the first antenatal visit, which typically occurs between the tenth and twelfth week of pregnancy. According to this definition, 28,467 (4.59%) infants were exposed anytime during pregnancy, 23,789 (3.83%) infants were exposed in a single trimester, and 4,678 (0.75%) were exposed in multiple trimesters.

We found commensurate results with the main analyses results using these alternative definitions (sTable III.8), suggesting that exposure misclassification did not bias our results.

sTable III.8. Adjusted associations with alternative exposure definitions

	Main analysis definition	Expanded definition	Restricted definition	Filled prescriptions or maternal reports definition
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Preterm birth				
Exposure anytime during pregnancy	1.38 (1.31, 1.45)	1.35 (1.29, 1.41)	1.37 (1.30, 1.44)	1.36 (1.29, 1.42)
Exposure in a single trimester	1.27 (1.20, 1.34)	1.25 (1.18, 1.31)	1.26 (1.19, 1.33)	1.24 (1.17, 1.31)
Exposure in multiple trimesters	1.97 (1.77, 2.18)	1.89 (1.72, 2.08)	1.97 (1.77, 2.18)	1.96 (1.77, 2.16)
Small for gestational age				
Exposure anytime during pregnancy	1.02 (0.93, 1.10)	1.01 (0.94, 1.09)	1.03 (0.94, 1.12)	1.01 (0.93, 1.10)
Exposure in a single trimester	0.95 (0.87, 1.04)	0.96 (0.88, 1.04)	0.96 (0.87, 1.06)	0.96 (0.87, 1.05)
Exposure in multiple trimesters	1.40 (1.17, 1.67)	1.34 (1.14,1.58)	1.40 (1.17, 1.67)	1.34 (1.12, 1.59)

Note. OR=odds ratio. CI=confidence interval.

SIII.8 Appendix: Sensitivity analyses evaluating the influence of type of opioid

First, we re-estimated adjusted associations in a subsample excluding 7,287 (1.17%) infants born to mothers with during pregnancy prescriptions of dextropropoxyphene (N02AC04 and N02AC54) because this medication is no longer prescribed in Sweden.

Second, we fit models in a subsample excluding 129 (0.02%) infants born to mothers with during pregnancy prescriptions of buprenorphine (N02AE01, N07BC01, N07BC51) or methadone (N07BC02) in case these infants were exposed to prescribed opioids for the treatment of opioid use disorder rather than pain.

We found the same pattern of results as in the main analyses (sTable III.9), suggesting that the findings are not largely driven by an opioid that is no longer prescribed in Sweden or by opioids that are prescribed for the treatment of opioid use disorder.

sTable III.9. Adjusted associations in the whole sample, in a subsample without filled dextropropoxyphene prescriptions during pregnancy, and in a subsample without methadone or buprenorphine prescriptions

	Whole sample (main analyses)	**Subsample without dextropropoxyphene**	**Subsample without filled methadone/ buprenorphine prescriptions**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Preterm birth			
Exposure anytime during pregnancy	1.38 (1.31, 1.45)	1.40 (1.32, 1.48)	1.37 (1.30, 1.44)
Exposure in a single trimester	1.27 (1.20, 1.34)	1.29 (1.21, 1.37)	1.27 (1.20, 1.34)
Exposure in multiple trimesters	1.97 (1.77, 2.18)	2.04 (1.80, 2.30)	1.94 (1.75, 2.16)
Small for gestational age			
Exposure anytime during pregnancy	1.02 (0.93, 1.10)	1.05 (0.95, 1.15)	1.02 (0.94, 1.11)
Exposure in a single trimester	0.95 (0.87, 1.04)	0.95 (0.85, 1.06)	0.95 (0.87, 1.05)
Exposure in multiple trimesters	1.40 (1.17, 1.67)	1.63 (1.34, 1.98)	1.42 (1.19, 1.69)

Note. OR=odds ratio. CI=confidence interval.

SIII.9 Appendix: Sensitivity analyses evaluating influence of inclusion of combination prescribed opioid analgesic medications

In order to evaluate whether exposure to medications other than POAs that are included in POA combination medications influenced the main analyses results, we re-estimated adjusted associations in a subsample excluding 19,697 (3.17%) infants born to mothers with filled prescriptions of combination POA medications (i.e., oxycodone/naloxone [N02AA55], buprenorphine/naloxone [N07BC51], morphine/antispasmodics [N02AG01], ketobemidone/antispasmodics [N02AG02], hydromorphone/antispasmodics [N02AG04], codeine combinations [N02AA59], and dextropropoxyphene combinations [N02AC54]).

We found the same pattern of results using this subsample as in the main analyses (sTable III.10), suggesting that the results were not driven by inclusion of combination POA medications.

sTable III.10. Adjusted associations in the whole sample and in a subsample without during pregnancy filled prescriptions of combination prescribed opioid analgesic medications

	Whole sample (main analyses)	**Subsample without combination prescribed opioid analgesic medications**
	OR (95% CI)	**OR (95% CI)**
Preterm birth		
Exposure anytime during pregnancy	1.38 (1.31, 1.45)	1.33 (1.21, 1.45)
Exposure in a single trimester	1.27 (1.20, 1.34)	1.27 (1.15, 1.41)
Exposure in multiple trimesters	1.97 (1.77, 2.18)	1.66 (1.33, 2.08)
Small for gestational age		
Exposure anytime during pregnancy	1.02 (0.93, 1.10)	0.98 (0.84, 1.14)
Exposure in a single trimester	0.95 (0.87, 1.04)	0.95 (0.82, 1.15)
Exposure in multiple trimesters	1.40 (1.17, 1.67)	1.16 (0.79, 1.71)

Note. OR=odds ratio. CI=confidence interval.

SIII.10 Appendix: Sensitivity analyses evaluating the role of polypharmacy

In our sample, approximately 15% of POA-exposed infants versus 4% of POA-unexposed infants were exposed to another psychiatric medication during pregnancy (Table 2). Therefore, it is possible that maternal use of additional psychiatric medications accounted for observed associations between POA exposure and increased risk for adverse birth outcomes in infants. Although we included polypharmacy as a covariate in the main analyses, to further assess whether exposure to polypharmacy was responsible for observed associations with POA exposure, we re-estimated adjusted associations in a subsample excluding 40,050 (6.45%) infants born to women prescribed other psychiatric medications during pregnancy. The results were commensurate with main analyses results (sTable III.11), suggesting that associations with POA exposure observed in main analyses were not driven by exposure to polypharmacy.

sTable III.11. Adjusted associations in a subsample without polypharmacy

	Adjusted associations in the whole sample (main analyses)	Adjusted associations in a subsample without polypharmacy
	OR (95% CI)	**OR (95% CI)**
Preterm birth		
Exposure anytime during pregnancy	1.38 (1.31, 1.45)	1.33 (1.25, 1.41)
Exposure in a single trimester	1.27 (1.20, 1.34)	1.26 (1.18, 1.34)
Exposure in multiple trimesters	1.97 (1.77, 2.18)	1.87 (1.63, 2.15)
Small for gestational age		
Exposure anytime during pregnancy	1.02 (0.93, 1.10)	1.01 (0.92, 1.10)
Exposure in a single trimester	0.95 (0.87, 1.04)	0.95 (0.86, 1.06)
Exposure in multiple trimesters	1.40 (1.17, 1.67)	1.39 (1.00, 1.75)

Note. OR=odds ratio. CI=confidence interval.

SIII.11 Appendix: Sensitivity analyses evaluating assumptions of sibling comparisons results

We performed two analyses to evaluate assumptions of sibling comparison designs.

First, to assess if the sibling comparison results would generalize to the entire population, which includes families without siblings, we estimated adjusted population-wide associations in a sample of 288,995 infants who had siblings in the dataset. We found population-wide associations in the subsample of siblings were commensurate to population-wide associations in the entire sample (sTable III.12), suggesting that siblings comparison results would generalize to families without siblings.

Second, to evaluate if carry-over effects (i.e., exposure in a prior pregnancy affecting subsequent pregnancies) influenced the sibling comparison results, we compared the risk for the outcomes among first-born cousins. The first-born cousin comparison results were comparable to the sibling comparison results (sTable III.13), suggesting that carry-over effects did not account for similar risk of the outcomes among differentially exposed siblings.

sTable III.12. Adjusted population wide associations among all infants and infants with siblings in the sample

	All infants (main analyses)	Siblings
	OR (95% CI)	**OR (95% CI)**
Preterm birth		
Exposure anytime during pregnancy	1.38 (1.31, 1.45)	1.33 (1.23, 1.45)
Exposure in a single trimester	1.27 (1.20, 1.34)	1.28 (1.17, 1.39)
Exposure in multiple trimesters	1.97 (1.77, 2.18)	1.69 (1.41, 2.03)
Small for gestational age		
Exposure anytime during pregnancy	1.02 (0.93, 1.10)	1.04 (0.90, 1.19)
Exposure in a single trimester	0.95 (0.87, 1.04)	0.99 (0.85, 1.15)
Exposure in multiple trimesters	1.40 (1.17, 1.67)	1.34 (0.97, 1.84)

Note. OR=odds ratio. CI=confidence interval.

sTable III.13. Sibling comparison and first-born cousin comparison associations

	Sibling comparison (main analyses)	First-born cousin comparison
	OR (95% CI)	**OR (95% CI)**
Preterm birth		
Exposure anytime during pregnancy	0.99 (0.85, 1.14)	1.01 (0.72, 1.40)
Exposure in a single trimester	0.99 (0.85, 1.15)	1.01 (0.70, 1.44)
Exposure in multiple trimesters	1.04 (0.70, 1.55)	1.03 (0.44, 2.41)
Small for gestational age		
Exposure anytime during pregnancy	0.91 (0.70, 1.19)	0.84 (0.54, 1.31)
Exposure in a single trimester	0.90 (0.69, 1.18)	0.79 (0.48, 1.28)
Exposure in multiple trimesters	1.22 (0.60, 2.48)	1.17 (0.38, 3.61)

Note. OR=odds ratio. CI=confidence interval.

SIII.12 Appendix: Sensitivity analyses evaluating associations with continuous outcomes

In order to evaluate whether an influence of POA exposure was not reflected in outcomes based on clinical cut-off values, we fit all main models predicting birth outcomes on continuous scales (i.e., gestation age [mean=278.79 days; standard deviation=12.19 days] and birth weight [mean=3552.51 grams; standard deviation=551.04 grams] adjusted for gestational age.

The results were consistent with the pattern of findings for dichotomous outcomes (sTable III.14). POA exposure was associated with reduced gestational age in unadjusted models and the associations were attenuated in subsequent models. For example, infants exposed in multiple trimesters, on average were born 5 days earlier than unexposed infants; however, siblings exposed in multiple trimesters had gestational periods that were less than 1 day shorter (0.73) than their unexposed siblings. These results suggest that confounding factors explain most of the observed associations between prenatal POA exposure and reduced gestational age. However, these analyses do not rule out a small causal effect of POA exposure on reducing gestational age.

Although infants exposed to POAs in multiple trimesters were on average 24 grams lighter than infants exposed to acetaminophen in multiple trimesters, across all other models POA exposure was not statistically significantly associated with reduced birth weight. These results suggest that POA exposure is unlikely to considerably increase the risk for reduced fetal growth.

sTable III.14. Associations with continuous outcomes

	Model 1: Unadjusted	**Model 2: Adjusted**	**Model 3: Comparative safety**	**Model 4: Before-pregnancy-only comparison**	**Model 5: Sibling comparison**
	B **(95% CI)**	***B*** **(95% CI)**	***B*** **(95% CI)**	***B*** **(95% CI)**	***B*** **(95% CI)**
Gestational age (days)					
Exposure anytime during pregnancy	-2.45 (-2.59, -2.30)	-1.95 (-2.10, -1.81)	-1.10 (-1.38, -0.81)	-0.46 (-0.71, -0.22)	-0.33 (-0.60, -0.06)
Exposure in a single trimester	-1.93 (-2.09, -1.77)	-1.93 (-2.09, -1.77)	0.11 (-0.16, 0.39)	-0.27 (-0.52, -0.01)	-0.31 (-0.58, -0.03)
Exposure in multiple trimesters	-5.18 (-5.54, -4.82)	-5.18 (-5.54, -4.82)	-2.38 (-2.81, -1.95)	-2.35 (-2.92, -1.77)	-0.73 (-1.49, 0.03)
Birth weight (grams) adjusted for gestational age					
Exposure anytime during pregnancy	30.39 (25.00, 35.78)	21.60 (16.34, 26.85)	11.49 (1.79, 21.19)	4.73 (-3.89, 13.35)	4.81 (-3.67, 13.29)
Exposure in a single trimester	33.66 (27.82, 39.51)	26.22 (20.54, 31.90)	19.30 (9.93, 28.67)	5.64 (-3.19, 14.46)	5.53 (-3.18, 14.24)
Exposure in multiple trimesters	12.85 (-0.46, 26.16)	-5.67 (-18.64, 7.31)	-24.40 (-39.12, -9.69)	-4.09 (-24.32, 16.14)	-4.15 (-27.98, 19.69)

Note. *B*=beta weight. CI=confidence interval.

SIII.13 Appendix: Sensitivity analyses evaluating the influence of missing data

Our target sample included 688,932 infants. We excluded approximately 10% of this sample (68,474 infants) with missing data on covariates from the target sample to create the analytic sample. In response to review's feedback, we conducted sensitivity analyses to evaluate the influence of missing data.

First, we estimated covariate adjusted associations between absence of data and POA exposure in the target sample. Absence of data was not associated with prescriptions anytime during pregnancy after adjusting for all measured covariates in our target sample (OR=1.03, 95% CI:0.98-1.08), indicating that covariate adjustment helped minimize potential bias from missing data.

Second, in the analytic sample, we only adjusted for covariates with complete data. These analyses showed commensurate results to the main analyses adjusted associations (sTable III.15). Then, we again only adjusted for covariates with complete data, but this time we conducted the analyses in the target sample with no missing data. Again, we found commensurate associations (sTable III.15). These results indicate that excluding infants with missing covariate data did not bias our results.

sTable III.15. Adjusted associations in the target and analytic samples

	Adjusted for all covariates in the analytic sample (main analyses)	Adjusted only for covariates with complete data[a] in the target sample	Adjusted only for covariates with complete data[a] in the analytic sample
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Preterm birth			
Exposure anytime during pregnancy	1.38 (1.31, 1.45)	1.40 (1.33, 1.46)	1.42 (1.35, 1.49)
Exposure in a single trimester	1.27 (1.20, 1.34)	1.29 (1.22, 1.36)	1.30 (1.22, 1.37)
Exposure in multiple trimesters	1.97 (1.77, 2.18)	1.97 (1.79, 2.18)	2.07 (1.87, 2.30)
Small for gestational age			
Exposure anytime during pregnancy	1.02 (0.93, 1.10)	1.06 (0.98, 1.14)	1.06 (0.98, 1.15)
Exposure in a single trimester	0.95 (0.87, 1.04)	0.98 (0.90, 1.07)	0.98 (0.89, 1.08)
Exposure in multiple trimesters	1.40 (1.17, 1.67)	1.48 (1.26, 1.75)	1.50 (1.26, 1.79)

Note. OR=odds ratio. CI=confidence interval. [a]Models adjusted for parity; year of birth; exposure to other psychiatric medications during pregnancy; maternal opioid use disorder, non-opioid substance use disorder, schizophrenia or bipolar disorder, definite or uncertain suicide attempt, and any criminal conviction before conception; and maternal age at childbearing.

SIII.14 Appendix: Prevalence of the covariates stratified by exposure status in the target sample

In Table 1, we reported prevalence of background characteristics among unexposed infants and infants exposed to POAs anytime during pregnancy. sTable III.16 also reports background characteristics among infants exposed to POAs in a single-trimester and infants exposed to POAs in multiple-trimesters.

sTable III.16. Prevalence of the covariates stratified by exposure status in the target sample

	Unexposed (n=658,580 [95.59%])	**Ever Exposed (n=30,352 [4.41%])**	**Single-trimester exposure (n=25,544 [3.71%])**	**Multiple-trimester exposure (n=4,808 [0.70%])**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Pregnancy-related characteristics				
Birth order				
1st	296455 (45.01)	11883 (39.15)	10275 (40.22)	1608 (33.44)
2nd	241854 (36.72)	10884 (35.86)	9230 (36.13)	1654 (34.40)
3rd or higher	120271 (18.26)	7585 (24.99)	6039 (23.64)	1546 (32.15)
Year of birth				
2007 to 2009	246792 (37.47)	11016 (36.29)	9195 (36.00)	1821 (37.87)
2010 to 2013	411788 (62.53)	19336 (63.71)	16349 (64.00)	2987 (62.13)
Maternal smoking during the first trimester				
None	596358 (90.55)	25881 (85.27)	22143 (86.69)	3738 (77.75)
Moderate(1-9 cigarettes/day)	30513 (4.63)	2455 (8.09)	1852 (7.25)	603 (12.54)
High(≥10 cigarettes/day)	8409 (1.28)	918 (3.02)	648 (2.54)	270 (5.62)
Missing	23300 (3.54)	1098 (3.62)	901 (3.53)	197 (4.10)
Exposure to other psychiatric medications	28432 (4.32)	4695 (15.47)	3938 (15.42)	1814 (37.73)
Maternal characteristics				
Opioid use disorder before conception	468 (0.07)	123 (0.41)	54 (0.21)	69 (1.44)
Non-opioid substance use disorder before conception	10298 (1.56)	960 (3.16)	683 (2.67)	277 (5.76)
Schizophrenia or bipolar disorder before conception	2576 (0.39)	285 (0.94)	217 (0.85)	68 (1.41)
Definite or uncertain suicide attempt before conception	11181 (1.70)	1247 (4.11)	926 (3.63)	321 (6.68)
Any criminal convictions before conception	43190 (6.56)	3352 (11.04)	2520 (9.87)	832 (17.30)
Age at year of birth				
Less than 19 years	6797 (1.03)	188 (0.62)	168 (0.66)	20 (0.42)
20 to 29 years	256894 (39.01)	11526 (37.97)	9901 (38.76)	1625 (33.80)
30 to 39 years	362436 (55.03)	16858 (55.54)	14054 (55.02)	2804 (58.32)
40 to 45 years	31600 (4.80)	1736 (5.72)	1384 (5.42)	352 (7.32)
46 years and older	853 (0.13)	44 (0.14)	37 (0.14)	7 (0.15)
Highest level of education at year of birth				
Less than 9 years	19895 (3.02)	865 (2.85)	755 (2.96)	110 (2.29)
9 years	50739 (7.70)	3729 (12.29)	2944 (11.53)	785 (16.33)
1 to 3 years upper secondary	239629 (36.39)	13022 (42.90)	10739 (42.04)	2283 (47.48)
Any post-secondary or postgraduate	332690 (50.52)	12301 (40.53)	10732 (42.01)	1569 (32.63)
Missing	15629 (2.37)	435 (1.43)	374 (1.46)	61 (1.27)
Country of origin				

Sweden	502636 (76.32)	24079 (79.33)	19997 (78.28)	4082 (84.90)
Missing	98 (0.01)	1 (0.00)	1 (0.00)	0 (0.00)
Paternal characteristics				
Opioid use disorder before conception	984 (0.15)	102 (0.34)	72 (0.27)	32 (0.67)
Non-opioid substance use disorder before conception	11554 (1.75)	832 (2.74)	635 (2.49)	197 (4.10)
Schizophrenia or bipolar disorder before conception	1968 (0.30)	144 (0.47)	110 (0.43)	34 (0.71)
Definite or uncertain suicide attempt before conception	7980 (1.21)	474 (1.56)	379 (1.48)	95 (1.98)
Any criminal convictions before conception	120387 (18.28)	7117 (23.45)	5698 (22.31)	1419 (29.51)
Less than 19 years				
20 to 29 years	2023 (0.31)	67 (0.22)	61 (0.24)	6 (0.12)
30 to 39 years	157717 (23.95)	7352 (24.22)	6280 (24.59)	1072 (22.30)
40 to 45 years	377775 (57.36)	17021 (56.08)	14350 (56.18)	2671 (55.55)
46 years and older	79403 (12.06)	3939 (12.98)	3221 (12.61)	718 (14.93)
Less than 19 years	27724 (4.21)	1346 (4.43)	1121 (4.39)	225 (4.68)
Missing	13938 (2.12)	627 (2.07)	511 (2.00)	116 (2.41)
Highest level of education at year of birth				
Less than 9 years	17865 (2.71)	788 (2.60)	681 (2.67)	107 (2.23)
9 years	60313 (9.16)	3432 (11.31)	2778 (10.88)	654 (13.60)
1 to 3 years upper secondary	293777 (44.61)	15014 (49.47)	12514 (48.99)	2500 (52.00)
Any post-secondary or postgraduate	259281 (39.37)	9985 (32.90)	8620 (33.75)	1365 (28.39)
Missing	27344 (4.15)	1133 (3.73)	951 (3.72)	182 (3.79)
Country of origin				
Sweden	492997 (74.86)	23367 (76.99)	19486 (76.28)	3881 (80.72)
Missing	14042 (2.13)	629 (2.07)	512 (2.00)	117 (2.43)
Other familial and socioeconomic characteristics				
Parental cohabitation status at birth				
Parents not cohabitating at birth	39845 (6.05)	2302 (7.58)	1839 (7.20)	463 (9.63)
Missing	24936 (3.79)	1194 (3.93)	998 (3.91)	196 (4.08)
Family income at year of birth				
1st quintile (lowest income)	55036 (8.36)	2183 (7.19)	1798 (7.04)	385 (8.01)
2nd quintile	85747 (13.02)	4319 (14.23)	3575 (14.00)	744 (15.47)
3rd quintile	190101 (28.87)	9292 (30.61)	7757 (30.37)	1535 (31.93)
4th quintile	222018 (33.71)	10098 (33.27)	8555 (33.49)	1543 (32.09)
5th quintile (highest income)	105678 (16.05)	4460 (14.69)	3859 (15.11)	601 (12.50)
Missing	2005 (0.30)	39 (0.13)	34 (0.13)	5 (0.10)
Neighborhood deprivation at year of birth				
1st quintile (least)	96203 (14.61)	4179 (13.77)	3534 (13.83)	645 (13.42)

2nd quintile	113124 (17.18)	5037 (16.60)	4248 (16.63)	789 (16.41)
3rd quintile (reference)	118578 (18.01)	5379 (17.72)	4540 (17.77)	839 (17.45)
4th quintile	140301 (21.30)	6532 (21.52)	5444 (21.31)	1088 (22.63)
5th quintile (most)	190374 (28.91)	9225 (30.39)	7778 (30.45)	1447 (30.10)
Missing	1189 (0.18)	43 (0.14)	34 (0.13)	9 (0.19)

SIII.15 Appendix: Prevalence of preterm birth and small for gestational age among all exposure and comparison groups.

In order to help interpret main analysis odds ratios, sTable III.17 presents prevalence of preterm birth and small for gestational age among exposure and comparison groups.

sTable III.17. Prevalence of preterm birth and small for gestation age infants among all exposure and comparison groups

	Exposed to prescribed opioid analgesics during pregnancy (n=27,559)	**Unexposed to prescribed opioid analgesics during pregnancy (n=592,899)**	**Exposed to pure acetaminophen during pregnancy (n=13,116)**	**[a]Exposed to prescribed opioid analgesics before pregnancy only (n=18,883)**	**Sibling exposed to prescribed opioid analgesics during pregnancy (n=9,386)**	**Sibling unexposed to prescribed opioid analgesics during pregnancy (n=10,103)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Preterm birth	1771 (6.43)	26323 (4.44)	703 (5.36)	1061 (5.62)	481 (5.12)	544 (5.38)
Small for gestational age	694 (2.19)	12519 (2.11)	317 (2.42)	415 (2.20)	158 (1.68)	202 (2.00)

IV. Paper 3:

A Population-based study of concurrent prescriptions of opioid analgesic and selective-serotonin reuptake inhibitor medications during pregnancy and risk for adverse birth outcomes

Citation:

Sujan, A.C., Rickert, M.E., Quinn, P.D., Ludema, C., Wiggs, K.K., Lichtenstein, P., Larsson, H., Oberg, A.S., D'Onofrio, B.M. (under review). *A Population-based study of concurrent prescriptions of opioid analgesic and selective-serotonin reuptake inhibitor medications during pregnancy and risk for adverse birth outcomes.*

Abstract

Background: Pregnant women with health conditions that cause pain often also have mental health problems, such as depressive and anxiety disorders. These comorbid conditions may cause women to use multiple medications during pregnancy, although the safety of such practice is poorly understood.

Objective: The objective of this study was to investigate the influence of combined prescriptions of opioid analgesics and selective-serotonin reuptake inhibitor (SSRI) antidepressants during pregnancy on two adverse birth outcomes.

Method: We analyzed a Swedish population-based sample of 688,914 births between 2007 and 2013. Using national registers, we obtained data on filled medication prescriptions, birth outcomes, and a wide range of parental characteristics, including indices of health and sociodemographic characteristics.

We estimated risks of preterm birth and small for gestational age following independent or combined prescriptions of the two medications compared to women without filled prescriptions for either medication. We adjusted for confounding factors using inverse probability of treatment weights.

Results: Preterm birth risk was higher among women with opioid analgesic prescriptions only (5.9%; risk ratio[RR]=1.3, 95% confidence interval[CI]:1.2,1.3), SSRIs only (6.2%; RR=1.3, 95% CI:1.3,1.4), and both medications (7.8%; RR=1.7, 95% CI:1.5,2.0) compared to unexposed women (4.6%). The interaction between the medications on preterm birth was small and not statistically significant (risk difference[RD]=0.4; relative excess risk due to the interaction[RERI]=0.1, 95% CI:-0.2, 0.3; RR=1.0, 95% CI: 0.9, 1.2).

Small for gestational age risk was approximately 2% across all groups, and there was no interaction between the medications on small for gestational age risk (RD=0.3; RERI=0.2, 95% CI:-0.2, 0.5; RR=1.2, 95% CI: 0.9, 1.5).

Conclusions: These findings have clinical relevance as they indicate that compared to pregnant women without opioid analgesic and SSRI prescriptions, the risks of two adverse birth outcomes are not substantially higher among pregnant women prescribed only one of the medications alone or both medications concurrently.

Introduction

Clinical guidelines recommend that pregnant women limit the number of different medications they use.[1] However, in practice pregnant women often have comorbid conditions, which may cause them to use multiple medications.[2] Notably, individuals prescribed opioids for pain are more likely to also be prescribed selective-serotine reuptake inhibitor (SSRI) medications,[3,4] which are commonly used to treat depression and anxiety.[5] In vitro research using human liver tissue suggests that SSRIs decrease the metabolism of opioids;[6] and, patient data has shown increased opioid plasma concentrations after SSRI administration.[7] The potential for opioid/SSRI interactions is particularly concerning among pregnant women because of possible harmful effects on developing offspring.

Studies evaluating opioids and SSRIs prescribed separately during pregnancy suggest that both medications may result in small increased risks of adverse birth outcomes.[8,9] A few studies have evaluated combination opioid and SSRI prescriptions during pregnancy on neonatal abstinence syndrome and have suggested that concomitant use is associated with a higher risk of neonatal abstinence syndrome[10] and are more severe and persistent symptoms.[11,12] Research into the potential influence of combined prescription of opioids and SSRIs on more common adverse birth outcomes, such as preterm birth and reduced fetal growth, is remarkably lacking; and, the existing studies have been limited by low statistical power.[11,13]

Moreover, based on the research to date, it is unclear the extent to which observed associations are due to a causal influence versus confounding factors. Women who are prescribed multiple medications during pregnancy are likely to have additional risk factors for adverse birth outcomes compared with women who are prescribed fewer medications during pregnancy. For example, compared with pregnant women who are only prescribed opioids,

pregnant women who are prescribed opioids plus another medication are more likely to be older and have more severe pain, psychiatric disorders, and substance use disorder.[10] As a result, observed associations between maternal prescriptions of multiple medications during pregnancy and adverse birth outcomes could be due to confounding factors.

Consistent with calls for research to examine consequences of concurrent medication prescriptions during pregnancy,[14] the objective of the present study was to investigate the influence of combined prescription of opioid analgesics and SSRIs during pregnancy on two common adverse birth outcomes – preterm birth and reduced fetal growth. This study builds on previous studies that separately examined associations with during pregnancy prescriptions of opioid analgesics and SSRIs, including our own work analyzing the same population-based sample used in the present study.[8,9]

Methods

Cohort selection

We obtained a population-based dataset by linking information from seven Swedish registers: (1) the Multi-Generation Register includes biological relationships for all individuals residing in Sweden since 1961;[15] (2) the Prescribed Drug Register (PDR) includes anatomical therapeutic class (ATC) codes for filled prescription medication since July 2005;[16,17] (3) the Medical Birth Register (MBR) includes information on 96 to 99% of births since 1973;[18-20] (4) the National Patient Register includes diagnoses from all hospital admissions since 1987 and specialist outpatient care since 2001;[21,22] (5) the National Crime Register includes criminal convictions since 1973;[23,24] (6) the Education Register includes highest level of completed formal education through 2013;[25] and, (7) the integrated database for labor market research includes annual socio-economic data for each individual since 1990.[26]

We started with a population-based sample of 711,986 births in Sweden July 1st 2007 to December 31st, 2013 and sequentially dropped 2,648 stillbirths, 107 records with invalid maternal identifiers, 6 pregnancies with missing sex, 19,844 multiple births, 173 missing gestational age, and 294 births where the prescribed opioid was likely to have been used to treat opioid use disorder (see below; our research question concerned opioids prescribed for pain treatment). The resulting sample included 688,914 singleton births.

Measures

Medications exposures. We defined medication exposure as prescriptions filled 90 days before conception through birth. We included the 90 day window before conception because in Sweden the maximum amount of medication prescribed is typically for 3 month periods.[27] We approximated conception date as birth date minus gestational age plus 14 days because of the convention of dating pregnancy from last menstrual period. The estimated gestational age recorded in the MBR was predominantly based on ultrasound measurement in the 18th to 20th week of pregnancy. Approximately 95% of all pregnant women in Sweden undergo at least one ultrasound.[28]

Opioids included buprenorphine and methadone prescribed as analgesics, as well as all other opioids (sTable IV.1 includes ATC codes). We used criteria identified in prior research (i.e., age of patient, route of administration and details of the dispensing method, prescriber, clinic, and patient age) to distinguish buprenorphine/methadone prescribed as analgesics from buprenorphine/methadone prescribed for opioid use disorder treatment.[29,30] The types of clinics prescribing the opioids are described in sTable IV.2. SSRIs included medications with ATC codes beginning with N06AB. We created four mutually exclusive exposure groups based on the prescriptions filled: opioid only (opioid and no SSRI), SSRI only (SSRI and no opioid), both

opioid and SSRI, and no record of either medication.

Background characteristics. We identified a range of background characteristics that could confound associations between medication use during pregnancy and adverse birth outcomes. Pregnancy-related characteristics included filled prescriptions for other psychiatric medications in the period 90 days before conception to birth (sTable IV.1 includes medications and ATC codes), as well as birth order, birth year, and maternal report of smoking at the first antenatal visit.

Maternal and paternal characteristics included inpatient and outpatient ICD diagnoses made prior to conception of non-bipolar mood disorder, anxiety disorders, opioid use disorder, non-opioid substance use disorders, schizophrenia or bipolar disorder, certain or uncertain suicide attempts;[31] any criminal convictions prior to conception; age at birth; highest level of education at year of birth; and country of origin. Previous research has validated the ICD-coded psychiatric diagnoses[32,33] and shown high predictive validity for the criminality measure.[34,35]

Other familial and socio-economic characteristics included maternal report of parental cohabitation at the first antenatal visit, and family income and neighborhood deprivation score in the year of the birth. Neighborhood deprivation score was a derived variable based on principal component analysis of several yearly indicators for geographical areas constructed to delineate socially homogenous areas. The score consisted of proportions of welfare recipients, unemployed individuals, immigrants, divorced individuals, and individuals with low educational attainment and measures of residential mobility, crime rates, and neighborhood disposable income. Previous research has found the neighborhood deprivation measure is associated with criminality and substance use disorders.[36]

Birth outcomes. We predicted preterm birth, which was defined as birth before 37

gestational weeks. To assess fetal growth, we also predicted small for gestational age, which was defined as birth weight less than two standard deviations below the expected fetal weight for gestational age.

Statistical analyses

We used SAS 9.4 to process and analyze the data.

Missing data. For the background characteristics with missing values, we used multiple imputation (five imputations) with the Markov chain Monte Carlo method to predict the missing values from all available information.[37-39] Notably, a limited number of background characteristics had missing values; and, across the included variables, missingness ranged from approximately 0% to 4% (Table IV.1).

Inverse probability of treatment weights. We created time-fixed, stabilized inverse probability of treatment weights (IPTWs) to adjust for potential confounding factors in subsequent analyses. We used logistic regression to predict the probability of exposure given potential confounders in the study sample. Each individual was then assigned a weight equal to the inverse of the predicted probability of their exposure status (given covariates), multiplied by the overall sample probability of their exposure status (to stabilize the weights). In order to eliminate the influence of cases with extreme weights,[40] we truncated the weights at the 1st and 99th percentiles. The resulting weights ranged from 0.18 to 1.79 and had a mean of 0.99.

Main analysis. For our main analysis, we used generalized linear models with a log link and binomial distribution to predict the risk (prevalence) of the outcomes according to exposure status (sTable IV.3 includes risk measure formulas). The regression was weighted by IPTWs to adjust for potential confounding and estimated separately in each of the five imputed datasets with the results averaged across the datasets. We obtained contrasts between the exposed

(opioids only, SSRIs only, or both opioids and SSRIs) and the unexposed on the absolute (risk difference) and relative (risk ratio) scales. We calculated risk differences from the predicted average risks of each group and obtained risk differences directly from the (exponentiated) regression coefficients. To assess potential interaction, we considered whether the effect of both medications was greater than could be expected from combining the independent effects of each medication. We calculated risk difference interaction estimates to assess additive interactions and risk ratio interaction estimates to assess multiplicative interactions. To obtain a statistical test for the additive interaction, we used the model-based risk ratios to estimate the relative excess risk due to interaction (RERI).

Ethics approval

This study used data from national Swedish registers. By Swedish law, informed consent was not necessary. The study was approved by the institutional review board at Indiana University (reference number: 1404771406A003; approval date: 2019-09-09) and the regional ethical review board in Stockholm, Sweden (reference number: 2013/862-31/5; approval date: 2013-09-12).

Results

Table IV.1 presents demographic characteristics stratified by exposure group.

Preterm birth

Compared to unexposed women (4.6%), women prescribed both SSRIs and opioids had the highest risk of preterm labor (9.4%), followed by women only prescribed opioids (6.3%) and then women only prescribed SSRIs (6.5%). Adjusting for differences in background factors did not change the risk for preterm birth among unexposed women (4.6%) but did reduce risk estimates among women prescribed both medications (7.8%; risk difference [RD]=3.2%),

opioids only (5.9%; RD=1.3%), and SSRIs only (6.2%; RD=1.6%; Table IV.2 includes risk ratios and their 95% confidence intervals). Importantly, while there was a small additive interaction with combined prescriptions (RD=0.4%), this additive interaction may not be clinically significant and also was not statistically significant when expressed through the RERI (0.09, 95% CI -0.17, 0.34). Moreover, there was no interaction on the multiplicative scale (RR=1.00, 95% CI 0.85, 1.17).

Small for gestational age

Both before (Table IV.1) and after adjustment for background characteristics (Table IV.3), small for gestational age risk was approximate 2% across all exposure groups ($RD_{opioid\ and\ SSRI}$=0.3%; RD_{opioid}=-0.0%; RD_{SSRI}=0.0%; Table IV.3 shows risk ratios and their 95% confidence intervals). There was a small additive interaction with combined prescriptions (RD=0.3%), which was not statistically significant when expressed through RERI (RERI=0.15, 95% CI:-0.16, 0.47). There was also a small but not statistically significant interaction on the multiplicative scale (RR=1.15, 95% CI: 0.87, 1.52).

Discussion

Principle findings

In a population-based sample of 688,914 Swedish births occurring between 2007 and 2013, we evaluated the separate and combined risk of maternal prescriptions of opioids for the treatment of pain and SSRI antidepressants during pregnancy on the risk of children being born preterm or small for their gestational age. We found that compared with unexposed women, women prescribed either opioids or SSRIs alone were at a small increased risk for having a child born preterm but were not at increased risk for having a child born small for gestational age. We also found the interaction between opioid and SSRI prescriptions on preterm birth was quite

small on the additive scale and not present on the multiplicative scale. Similarly, the interaction between opioid and SSRI prescriptions on small for gestational age was also small and not statistically significant on both the additive and multiplicative scales.

Strengths of the study

Our study had several noteworthy strengths. First, the large sample size allowed for more precise estimation than in previous studies. Second, our use of multiple imputation rather than a complete case analysis, helped reduce selection bias as those with missing data on some of the relevant covariates did not need to be excluded. Third, we considered the influence of confounding. To evaluate the influence of measured confounding, we used IPTW rather than traditional covariate adjustment. Traditional covariate adjustment that includes background characteristics as predictors in regression models can become unstable if exposed and unexposed differ greatly in their covariate distributions or if many covariates are used because each stratum in which the effect is estimated may contain very few individuals. IPTW methods avoid these potential problems by creating a pseudo-population in which background characteristics are similar among exposure groups, a property that would be expected if randomization had occurred.[41,42] We also believe that unmeasured confounding is unlikely to have biased our results. The estimates of associations with opioid-only exposure and SSRI-only exposure were similar in magnitude to those obtained in our previous studies, which were conducted in the same dataset and used several designs, including sibling comparisons, to adjust for unmeasured and measured confounding.[8,9] Fourth, we tested interactions on both the additive and multiplicative scale. Interaction typically are evaluated on the multiplicative scale; however, it is important to also test for interactions on the additive scale as interactions can be present on one scale but not

the other, and estimates on the additive indicate absolute risks, which are important to consider in clinical decision-making.[43]

Limitations of the data

Our study also had some limitations. First, our results may have been influenced by exposure misclassification because a filled prescription does not guarantee that the woman was taking the medication. Moreover, we do not know if women with filled prescriptions for both opioids and SSRIs during pregnancy used the medications at the same time. Second, we did not consider the dosage or duration of medication use. Third, we did not take into account timing of exposure in order to evaluate if there were sensitive periods of exposure during pregnancy. Fourth, although certain opioid and SSRI medications may be more prone to interactions, we could not examine specific medications due to how rare exposures were. For example, combination use of the opioid tramadol with an SSRI could be particularly problematic because tramadol affects both opioid and serotonin receptors.[44] Fifth, we do not know if our findings will generalize to countries outside of Sweden given between-country differences (e.g., higher prescribing rates of opioids and SSRIs in the US compared with Sweden).[8,45-47]

Interpretation

Our findings evaluating use of opioid analgesics or SSRIs alone are consistent with our own and other's previous research that also suggested that prenatal exposure to only opioid analgesics or only SSRIs is associated with a small increased risk of preterm birth [48-50] but not small for gestational age.[8,50-53]

Few previous studies had evaluated consequences of concurrent used of opioid analgesics and SSRIs during pregnancy on gestational age and fetal growth. Our findings that the interactions between the medications on both preterm birth and small gestational age were small

and not statistically significant was consistent with a study of 148 women using opioids in pregnancy that failed to find statically significant differences in gestational age and birth weight of those exposed (n=16) and unexposed (n=132) to antidepressants.[11] However, our findings were not consistent with another study using Swedish registry data that reported higher risk of preterm labor among women who had used both SSRIs and opioids in pregnancy (n=39) compared with women who had used SSRIs only (n=2,729).[13] However, it is important to note that due to the small sample sizes, it is not possible to distinguish whether the noted differences in this study were chance findings.

Conclusions

Public health experts have recommended focusing on absolute risks when considering clinical implications, particularly when considering clinical implications of exposure interactions.[43] Our findings may provide helpful information to women and their doctors considering opioid and SSRI use during pregnancy because they indicate that, compared to pregnant women without opioids and SSRI prescriptions, the risks of two adverse birth outcomes are not substantially higher among pregnant women prescribed only one of the medications alone or both medications concurrently. Assuming the entire observed association was due to a causal effect, the results indicate that opioid exposure alone would increase the prevalence of preterm birth by one percent and decrease the prevalence of small for gestational age by one-tenth of a percent; SSRI exposure alone would increase the prevalence of preterm birth by one percent and small for gestational age by one-tenth of a percent; and combined used of the two medications would not additionally change preterm birth prevalence but would increase small for gestational age prevalence by four-tenths of a percent. From a clinical decision-making standpoint, it is important to consider the severity of the adverse outcomes associated with a medication use – a

small increase risk in preterm birth or small for gestational age may be tolerable, particularly when considering the risk of untreated underlying maternal conditions.

Table IV.1. Prevalence of exposure groups, background characteristics, and outcomes in the target sample (n=688,914)

	Unexposed (n=628,608 [91.25%])	**Opioid only (n=35,080 [5.09%])**	**SSRI only (n=22,013 [3.20%])**	**Both (n=3,213 [0.47%])**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Outcomes				
Preterm birth	28717 (4.57)	2198 (6.27)	1440 (6.54)	302 (9.40)
Small for gestational age	14012 (2.23)	796 (2.27)	510 (2.32)	89 (2.77)
Pregnancy-related characteristics				
Exposure to other psychiatric medications				
Benzodiazepines	5869 (0.93)	2245 (6.4)	3515 (15.97)	1042 (32.43)
Non-benzodiazepine anxiolytics	2859 (0.45)	554 (1.58)	1876 (8.52)	399 (12.42)
Non-benzodiazepine hypnotics/sedatives	4182 (0.67)	1259 (3.59)	1943 (8.83)	559 (17.4)
Non-SSRI antidepressants	3652 (0.58)	1098 (3.13)	1767 (8.03)	459 (14.29)
Antipsychotics	1030 (0.16)	175 (0.50)	606 (2.75)	128 (3.98)
Mood stabilizers/anticonvulsants	2870 (0.46)	597 (1.7)	791 (3.59)	258 (8.03)
Attention-deficit/hyperactivity disorder medications	778 (0.12)	165 (0.47)	315 (1.43)	68 (2.12)
Substance use disorders medications	458 (0.07)	105 (0.30)	109 (0.50)	37 (1.15)
Birth order				
1st	282759 (44.98)	14116 (40.24)	10191 (46.3)	1263 (39.31)
2nd	232070 (36.92)	12496 (35.62)	7156 (32.51)	1010 (31.43)
3rd or higher	113779 (18.10)	8468 (24.14)	4666 (21.20)	940 (29.26)
Year of birth				
2007 to 2009	236589 (37.64)	12799 (36.49)	7339 (33.34)	1080 (33.61)
2010 to 2013	392019 (62.36)	22281 (63.51)	14674 (66.66)	2133 (66.39)
Maternal smoking during the first trimester				
None	571075 (90.85)	30130 (85.89)	18516 (84.11)	2507 (78.03)
Moderate(1-9 cigarettes/day)	27886 (4.44)	2729 (7.78)	1956 (8.89)	391 (12.17)
High(≥10 cigarettes/day)	7372 (1.17)	979 (2.79)	791 (3.59)	184 (5.73)
Missing	22275 (3.54)	1242 (3.54)	750 (3.41)	131 (4.08)
Maternal characteristics				
Non-bipolar mood disorder prior to conception	10733 (1.71)	17.87 (5.09)	3389 (15.40)	717 (22.32)
Anxiety disorder prior to conception	8374 (1.33)	1350 (3.85)	4415 (20.06)	822 (25.58)
Opioid use disorder before conception	369 (0.06)	100 (0.29)	72 (0.33)	45 (1.40)
Non-opioid substance use disorder before conception	8711 (1.39)	985 (2.81)	1290 (5.86)	265 (8.25)
Schizophrenia or bipolar disorder before conception	1917 (0.3)	229 (0.65)	588 (2.67)	126 (3.92)
Definite or uncertain suicide attempt before conception	9402 (1.50)	1299 (3.70)	1427 (6.48)	293 (9.12)
Any criminal convictions before conception	39523 (6.29)	3741 (10.66)	2714 (12.33)	554 (17.24)
Age at year of birth				
Less than 19 years	6453 (1.03)	220 (0.63)	298 (1.35)	14 (0.44)
20 to 29 years	245658 (39.08)	13568 (38.68)	8051 (36.57)	1140 (35.48)
30 to 39 years	345983 (55.04)	19245 (54.86)	12228 (55.55)	1823 (56.74)
40 to 45 years	29711 (4.73)	1990 (5.67)	1403 (6.37)	232 (7.22)
46 years and older	803 (0.13)	57 (0.16)	33 (0.15)	4 (0.12)

Highest level of education at year of birth				
Less than 9 years	19268 (3.07)	1080 (3.08)	346 (1.57)	66 (2.05)
9 years	46827 (7.45)	4203 (11.98)	2887 (13.11)	544 (16.93)
1 to 3 years upper secondary	227474 (36.19)	15019 (42.81)	8691 (39.48)	1458 (45.38)
Any post-secondary or postgraduate	319717 (50.86)	14267 (40.67)	9892 (44.94)	1111 (34.58)
Missing	15322 (2.44)	511 (1.46)	197 (0.89)	34 (1.06)
Nationality				
Sweden	477060 (75.89)	27598 (78.67)	19305 (87.70)	2735 (85.12)
Missing	96 (0.02)	2 (0.01)	1 (0.00)	0 (0.00)
Paternal characteristics				
Non-bipolar mood disorder prior to conception				
Diagnoses	4931 (0.78)	490 (1.40)	434 (1.97)	78 (2.43)
Missing	13214 (2.10)	716 (2.04)	527 (2.39)	107 (3.33)
Anxiety disorder prior to conception				
Diagnoses	6786 (1.08)	648 (1.85)	538 (2.44)	119 (3.70)
Missing	13214 (2.10)	716 (2.04)	527 (2.39)	107 (3.33)
Opioid use disorder before conception				
Diagnoses	861 (0.14)	115 (0.33)	88 (0.40)	19 (0.59)
Missing	13214 (2.10)	716 (2.04)	527 (2.39)	107 (3.33)
Non-opioid substance use disorder before conception				
Diagnoses	10505 (1.67)	923 (2.63)	805 (3.66)	151 (4.70)
Missing	13214 (2.10)	716 (2.04)	527 (2.39)	107 (3.33)
Schizophrenia or bipolar disorder before conception				
Diagnoses	1785 (0.28)	143 (0.41)	153 (0.70)	31 (0.96)
Missing	13214 (2.10)	716 (2.04)	527 (2.39)	107 (3.33)
Definite or uncertain suicide attempts before conception				
Diagnoses	7395 (1.18)	533 (1.52)	439 (1.99)	85 (2.65)
Missing	13214 (2.10)	716 (2.04)	527 (2.39)	107 (3.33)
Any criminal convictions before conception				
Criminal convictions	113069 (17.99)	8177 (23.31)	5319 (24.16)	931 (28.98)
Missing	13214 (2.10)	716 (2.04)	527 (2.39)	107 (3.33)
Age at year of birth				
Less than 19 years	1897 (0.30)	81 (0.23)	109 (0.50)	3 (0.09)
20 to 29 years	150118 (23.88)	8618 (24.57)	5531 (25.13)	802 (24.96)
30 to 39 years	361479 (57.50)	19598 (55.87)	11998 (54.5)	1705 (53.07)
40 to 45 years	75489 (12.01)	4497 (12.82)	2898 (13.16)	458 (14.25)
46 years and older	26411 (4.20)	1570 (4.48)	950 (4.32)	138 (4.30)
Missing	13214 (2.10)	716 (2.04)	527 (2.39)	107 (3.33)
Highest level of education at year of birth				
Less than 9 years	17281 (2.75)	953 (2.72)	343 (1.56)	76 (2.37)
9 years	56757 (9.03)	4013 (11.44)	2515 (11.43)	456 (14.19)
1 to 3 years upper secondary	279346 (44.44)	17257 (49.19)	10531 (47.84)	1645 (51.20)
Any post-secondary or postgraduate	249092 (39.63)	11541 (32.9)	7754 (35.22)	878 (27.33)
Missing	26132 (4.16)	1316 (3.75)	870 (3.95)	158 (4.92)
Nationality				
Sweden	468810 (74.58)	26754 (76.27)	18190 (82.63)	2593 (80.70)
Missing	13315 (2.12)	719 (2.05)	529 (2.40)	107 (3.33)

Other familial and socioeconomic characteristics				
Parental cohabitation status at birth				
Parents not cohabitating at birth	36563 (5.82)	2602 (7.42)	2570 (11.67)	407 (12.67)
Missing	23844 (3.79)	1345 (3.83)	806 (3.66)	135 (4.20)
Family income at year of birth				
1st quintile	52196 (8.30)	2531 (7.21)	2174 (9.88)	315 (9.80)
2nd quintile	81187 (12.92)	4928 (14.05)	3382 (15.36)	563 (17.52)
3rd quintile (reference)	180668 (28.74)	10727 (30.58)	6959 (31.61)	1033 (32.15)
4th quintile	212608 (33.82)	11670 (33.27)	6888 (31.29)	948 (29.51)
5th quintile	101949 (16.22)	5224 (14.89)	2610 (11.86)	354 (11.02)
Missing	1958 (0.31)	46 (0.13)	36 (0.16)	4 (0.12)
Neighborhood deprivation at year of birth				
1st quintile	92484 (14.71)	4771 (13.6)	2734 (12.42)	393 (12.23)
2nd quintile	108076 (17.19)	5817 (16.58)	3737 (16.98)	531 (16.53)
3rd quintile (reference)	113084 (17.99)	6138 (17.5)	4140 (18.81)	593 (18.46)
4th quintile	133330 (21.21)	7566 (21.57)	5222 (23.72)	707 (22)
5th quintile	181634 (28.89)	10788 (30.75)	6180 (28.07)	989 (30.78)
Missing	1137 (0.18)	49 (0.14)	39 (0.18)	7 (0.22)

Table IV.2. Preterm birth

	Exposure groups				Opioid x SSRI interaction	
	Unexposed	**Opioid only**	**SSRI only**	**Both**	**Additive scale**	**Multiplicative scale**
Prevalence (%)	4.60	5.85	6.18	7.82	–	–
Risk difference (%)	–	1.25	1.57	3.21	0.39	–
Risk ratio (95% CI)	–	1.27(1.22,1.33)	1.34(1.27,1.42)	1.70(1.47,1.96)	[a]0.09(-0.17,0.34)	1.00(0.85, 1.17)

SSRI=selective serotonin reuptake inhibitor. CI=confidence interval. [a]Relative excess risk due to the interaction.

Table IV.3. Small for gestational age

	Exposure groups				Opioid x SSRI interaction	
	Unexposed	**Opioid only**	**SSRI only**	**Both**	**Additive scale**	**Multiplicative scale**
Prevalence (%)	2.23	2.22	2.24	2.57	–	–
Risk difference (%)	–	-0.01	0.01	0.34	0.34	–
Risk ratio (95% CI)	–	1.00(0.93,1.07)	1.00(0.91,1.11)	1.15(0.89,1.48)	[a]0.15(-0.16,0.47)	1.15(0.87,1.52)

SSRI=selective serotonin reuptake inhibitor. CI=confidence interval. [a]Relative excess risk due to the interaction.

References

1. Armstrong C. American College of Obstetricians and Gynecologists guidelines on psychiatric medication use during pregnancy and lactation. *Obstetrics & Gynecology.* 2008;78(6):772.
2. Peindl KS, Masand P, Mannelli P, Narasimhan M, Patkar A. Polypharmacy in pregnant women with major psychiatric illness: a pilot study. *J Psychiatr Pract.* 2007;13(6):385-392.
3. Quinn PD, Hur K, Chang Z, et al. Incident and long-term opioid therapy among patients with psychiatric conditions and medications: a national study of commercial health care claims. *Pain.* 2017;158(1):140-148.
4. Quinn PD, Rickert ME, Franck J, et al. Associations of mental health and family background with opioid analgesic therapy: a nationwide Swedish register-based study. *Pain.* 2019.
5. Wong J, Motulsky A, Eguale T, Buckeridge DL, Abrahamowicz M, Tamblyn R. Treatment Indications for Antidepressants Prescribed in Primary Care in Quebec, Canada, 2006-2015. *JAMA.* 2016;315(20):2230-2232.
6. Iribarne C, Picart D, Dreano Y, Berthou F. In vitro interactions between fluoxetine or fluvoxamine and methadone or buprenorphine. *Fundamental & clinical pharmacology.* 1998;12(2):194-199.
7. Bertschy G, Baumann P, Eap C, Baettig D. Probable metabolic interaction between methadone and fluvoxamine in addict patients. *Therapeutic drug monitoring.* 1994;16(1):42-45.

8. 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.

9. Sujan AC, Quinn PD, Rickert ME, et al. Maternal prescribed opioid analgesic use during pregnancy and associations with adverse birth outcomes: A population-based study. *PLOS Medicine.* 2019;16(12):e1002980.

10. Huybrechts KF, Bateman BT, Desai RJ, et al. Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications: cohort study. *Bmj-British Medical Journal.* 2017;358.

11. O'Connor AB, O'Brien L, Alto WA, Wong J. Does concurrent in utero exposure to buprenorphine and antidepressant medications influence the course of neonatal abstinence syndrome? *Journal of Maternal-Fetal & Neonatal Medicine.* 2016;29(1):112-114.

12. Kaltenbach K, Holbrook A, Coyle MG, et al. Predicting Treatment for Neonatal Abstinence Syndrome in Infants Born to Women Maintained on Opioid Agonist Medication. *Addiction (Abingdon, England).* 2012;107(0 1):45-52.

13. Kallen B, Reis M. Neonatal Complications After Maternal Concomitant Use of SSRI and Other Central Nervous System Active Drugs During the Second or Third Trimester of Pregnancy. *Journal of Clinical Psychopharmacology.* 2012;32(5):608-614.

14. Temming LA, Cahill AG, Riley LE. Clinical Opinion Clinical Management of Medications in Pregnancy and Lactation. *American journal of obstetrics and gynecology.* 2016;214(6):698-702.

15. Statistics Sweden. *Multi-Generation Register 2009 - A Description of Contents and Quality.* Örebro, Sweden2010.

16. National Board of Health and Welfare. *4 years with the Prescribed Drug Register [in Swedish].* Stockholm: National Board of Health and Welfare;2010.

17. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiology and drug safety.* 2007;16(7):726-735.

18. National Board of Health and Welfare. *The Swedish Medical Birth Register - A Summary of Content and Quality.* Stockholm: National Board of Health and Welfare;2003.

19. Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. *Scand J Soc Med.* 1990;18(2):143-148.

20. National Board of Health and Welfare. *Pregnancies, Deliveries and Newborn Infants - The Swedish Medical Birth Register 1973-2011, Assisted Reproduction, treatment 1991-2010 [in Swedish].* Stockholm2013.

21. National Board of Health and Welfare. *Quality and Content in the Patient Register - Inpatient care discharges 1964-2007 and outpatient (specialized care) visits 1997-2007 [in Swedish].* Stockholm: National Board of Health and Welfare;2009. 2009-125-15.

22. WHO. *International Classification of Diseases, World Health Organization WHO.* Geneva1992.

23. Fazel S, Grann M. The population impact of severe mental illness on violent crime. *Am J Psychiatry.* 2006;163(8):1397-1403.

24. BRÅ e. Kriminalstatistik 2010 [Criminal statistics]. . In: Västerås, ed2011.

25. Statistics Sweden. Education in Sweden 2009. . https://www.scb.se/statistik/_publikationer/UF0527_2009A01_BR_UF08BR0901.pdf. Published 2009. Updated February 21, 2014. Accessed.

26. LISA database. http://www.scb.se/Pages/List____257743.aspx. Accessed.

27. Soderberg KC, Laflamme L, Moller J. Newly initiated opioid treatment and the risk of fall-related injuries. A nationwide, register-based, case-crossover study in Sweden. *Cns Drugs.* 2013;27(2):155-161.

28. Hagenfeldt K, Alton V, Axelsson O, et al. Routine ultrasound examination during pregnancy - summary in English. Stockholm: The Swedish Council on Health Technology Assessment (SBU). 1998.

29. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC classification and DDD assignment 2014.* Oslo: Author;2013.

30. Abrahamsson T, Berge J, Ojehagen A, Hakansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment-A nation-wide register-based open cohort study. *Drug Alcohol Depend.* 2017;174:58-64.

31. Tidemalm D, Langstrom N, Lichtenstein P, Runeson B. Risk of suicide after suicide attempt according to coexisting psychiatric disorder: Swedish cohort study with long term follow-up. *BMJ.* 2008;337:a2205.

32. Kendler K, Sundquist K, Ohlsson H, et al. Genetic and familial environmental influences on the risk for drug abuse: A national swedish adoption study. *Arch Gen Psychiat.* 2012;69(7):690-697.

33. D'Onofrio BM, Rickert ME, Långström N, et al. Familial confounding of the associations between maternal smoking during pregnancy and offspring substance use and problems. *Archives of General Psychiatry.* 2012;69:1140-1150.

34. D'Onofrio BM, Singh AL, Iliadou A, et al. Familial confounding of the association between maternal smoking during pregnancy and offspring criminality: A population-based study in Sweden. *Archives of General Psychiatry.* 2010;67:529-538.

35. Frisell T, Lichtenstein P, Langstrom N. Violent crime runs in families: a total population study of 12.5 million individuals. *Psychol Med.* 2011;41(1):97-105.

36. Sariaslan A, Langstrom N, D'Onofrio B, Hallqvist J, Franck J, Lichtenstein P. The impact of neighbourhood deprivation on adolescent violent criminality and substance misuse: a longitudinal, quasi-experimental study of the total Swedish population. *Int J Epidemiol.* 2013;42(4):1057-1066.

37. Collins LM, Schafer JL, Kam CM. A comparison of inclusive and restrictive strategies in modern missing data procedures. *Psychological methods.* 2001;6(4):330-351.

38. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Statistical Methods in Medical Research.* 2007;16(3):199-218.

39. Moons KGM, Donders RART, Stijnen T, Harrell FE. Using the outcome for imputation of missing predictor values was preferred. *J Clin Epidemiol.* 2006;59(10):1092-1101.

40. Cole SR, Hernán MA. Constructing Inverse Probability Weights for Marginal Structural Models. *American Journal of Epidemiology.* 2008;168(6):656-664.

41. Thoemmes F, Ong AD. A Primer on Inverse Probability of Treatment Weighting and Marginal Structural Models. *Emerging Adulthood.* 2015;4(1):40-59.

42. Hernán M, Robins J. *Causal Inference.* Boca Raton: Chapman & Hall/CRC, forthcoming; 2019.

43. VanderWeele Tyler J, Knol Mirjam J. A Tutorial on Interaction. In. *Epidemiologic Methods.* Vol 32014:33.

44. Sansone RA, Sansone LA. Tramadol: seizures, serotonin syndrome, and coadministered antidepressants. *Psychiatry (Edgmont).* 2009;6(4):17-21.

45. Andrade SE, Reichman ME, Mott K, et al. Use of selective serotonin reuptake inhibitors (SSRIs) in women delivering liveborn infants and other women of child-bearing age within the US Food and Drug Administration's Mini-Sentinel program. *Archives of Womens Mental Health.* 2016;19(6):969-977.

46. Bateman BT, Hernandez-Diaz S, Rathmell JP, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. *Anesthesiology.* 2014;120(5):1216-1224.

47. Handal M, Engeland A, Ronning M, Skurtveit S, Furu K. Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: a population-based cohort study. *European Journal of Clinical Pharmacology.* 2011;67(9):953-960.

48. Huang H, Coleman S, Bridge JA, Yonkers K, Katon W. A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight. *Gen Hosp Psychiatry.* 2014;36(1):13-18.

49. Patrick SW, Dudley J, Martin PR, et al. Prescription Opioid Epidemic and Infant Outcomes. *Pediatrics.* 2015;135(5):842.

50. Sujan AC, Quinn PD, Rickert ME, et al. Maternal prescribed opioid analgesic use during pregnancy and risk for adverse birth outcomes: A population-based study *Plos Medicine.* in press.

51. Yazdy MM, Desai RJ, Brogly SB. Prescription Opioids in Pregnancy and Birth Outcomes: A Review of the Literature. *J Pediatr Genet.* 2015;4(2):56-70.

52. Einarson A, Choi J, Einarson TR, Koren G. Adverse effects of antidepressant use in pregnancy: an evaluation of fetal growth and preterm birth. *Depress Anxiety.* 2010;27(1):35-38.

53. El Marroun H, Jaddoe VW, Hudziak JJ, et al. Maternal use of selective serotonin reuptake inhibitors, fetal growth, and risk of adverse birth outcomes. *Arch Gen Psychiatry.* 2012.

sTable IV.1. Other psychiatric medication anatomical therapeutic class codes

Medication	Code
Opioids	
Morphine	N02AA01
Hydromorphone	N02AA03
Oxycodone	N02AA05
Oxycodone/naloxone	N02AA55
Codeine/acetaminophen	N02AA59
Ketobemidone	N02AB01
Fentanyl	N02AB03
Dextropropoxyphene	N02AC04
Buprenorphine	N02AE01, N07BC01, N07BC51
Morphine/antispasmodics	N02AG01
Ketobemidone/antispasmodics	N02AG02
Tramadol	N02AX02
Tapentadol	N02AX06
Acetaminophen/codeine	NO2BE51
Methadone	N07BC02
Selective-serotine reuptake inhibitors	N06AB
Other psychiatric medications	
Benzodiazepines	N05BA, N05CD, N05CF, N03AE01
Non-benzodiazepine anxiolytics	N05BB, N05BC, N05BD, N05BE, N05BX
Non-benzodiazepine hypnotics/sedatives	N05CA, N05CB,N05CC, N05CE, N05CH, N05CM, N05CX
Non -SSRI antidepressants	N06A excluding N06AB
Antipsychotics	N03A and N05AN01
Mood stabilizers/anticonvulsants	N05A excluding N05AN01
attention-deficit/hyperactivity disorder medications	N06BA01, N06BA02, N06BA04, N06BA09
Nicotine/alcohol use disorder medications	N07BA excluding N07BA02 and N07BB

sTable IV.2. Types of clinics prescribing opioid analgesic medications received by mothers in the period 90 days before pregnancy to birth

Clinic type	N (%)
Primary care	30180 (38.8)
Obstetrics and gynecology	19586 (25.18)
Maternity care	6355 (8.17)
Surgery	3444 (4.43)
Non-surgical orthopedics	3382 (4.35)
Emergency	1955 (2.51)
Internal medicine	2089 (2.69)
Anesthesiology	843 (1.08)
Non-surgical dental	1842 (2.37)
Neurology	855 (1.10)
Gastrointestinal	215 (0.28)
Psychiatry	886 (1.14)
Other	5841 (7.51)
Missing	312 (0.40)
Total	77785 (100)

sTable IV.3. Risk measure formulas

	Exposure groups				Opioid x SSRI interaction	
	Unexposed	**Opioid only**	**SSRI only**	**Both**	**Additive scale**	**Multiplicative scale**
Probability	P00	P10	P01	P11	–	–
Risk difference	–	RD_{opioid}= P10-P00	RD_{SSRI}= P01-P00	RD_{Both}= P11-P00	$RD_{opioidxSSR}$= IRD_{Both}-(RD_{opioid}+RD_{SSRI})	–
Risk ratio	–	RR_{opioid}= P10/P00	RR_{SSRI}= P01/P00	RR_{Both}= P11/P00	RERI= RR_{Both}-(RR_{opioid}+RR_{SSRI})+1	$RR_{opioidxSSR}$ = RR_{Both}/(RR_{opioid}*RR_{SSRI})

SSRI=selective serotonin reuptake inhibitor. RD=risk difference. RR=risk ratio. RERI=relative excess risk due to the interaction.

V. Summary and Overall Discussion

Aims

My dissertation research aimed to test the consequences of prenatal exposure to antidepressant and prescribed opioid analgesic (POA) medications on adverse birth outcomes and neurodevelopmental problems. To do this, I analyzed a population-based dataset of births in Sweden and sought converging evidence from multiple observational methods that targeted both *measured* and *unmeasured* confounding factors.

Main findings

In general, my findings did not provide strong support for a causal effect of these medications, particularly for associations with the neurodevelopmental outcomes. My first study evaluated risk of preterm birth (PTB), small for gestational age (SGA; a measure of fetal growth), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) following prenatal exposure to antidepressants in a population-based sample of approximately 1.5 million Swedish offspring born 1996 to 2012. The results suggested that observed associations between prenatal antidepressant exposure and all four outcomes were largely due to unmeasured confounding factors, though I could not rule out a small independent association with increased risk of PTB. After this study was published, several additional studies, reviews, and meta-analyses were published evaluating the role of confounding, particularly unmeasured confounding, for associations between prenatal antidepressant exposure and neurodevelopmental outcomes; and, the results of my study are consistent with the other studies that also targeted unmeasured confounding.[1-8] My results are also consistent with the sparse research that has also tested the role of unmeasured confounding in associations between prenatal antidepressant exposure and adverse birth outcomes.[9]

My second study evaluated the risk of PTB and SGA following prenatal exposure to POAs in a Swedish population-based sample of approximately 600,000 pregnancies occurring between 2007 and 2013. My results are consistent with previous studies that reported associations between POA exposure and adverse birth outcomes[10] as I found that POA prescriptions during pregnancy, particularly prescriptions in multiple trimesters, were associated with increased risk for PTB and SGA. My results expanded upon previous research by indicating that the observed associations with both PTB and SGA were largely due to unmeasured confounding factors.

My third study evaluated combined exposure to POAs and selective serotonin reuptake inhibitor (SSRI) antidepressants on risk for PTB and SGA in a sample of approximately 700,000 pregnancies occurring in Sweden between 2007 and 2013. The results suggested that the two medications do not interact to increase the risk of either adverse birth outcomes. These results are consistent with one study that failed to find statically significant differences in gestational age and birth weight of those exposed (n=16) and unexposed (n=132) to antidepressants,[11] but are not consistent with another study that reported higher risk of preterm birth among women who had used both SSRIs and opioids in pregnancy (n=39) compared with women who had used SSRIs only (n=2,729).[12] However, it is important to note that due to the small sample sizes, it is difficult to draw strong conclusions from the two previous studies.

Strengths

There were several notable general strengths of my studies. First, they were conducted on a large, population-based sample, which provided adequate statistical power to examine rare-yet-serious outcomes. Second, I used advanced methods to assess the role of confounding. Studies one and two not only adjusted for a wide range of measured confounding factors, but also used

several methods to test the role of unmeasured confounding; and, study three used inverse probability of treatment weighting to adjust for numerous measured confounding factors. Third, I conducted extensive sensitivity analyses to test the several assumptions inherent to the methods I used. For example, the sensitivity analyses suggested that sibling comparisons results were not due to carry over effects (i.e., exposure in a prior pregnancy affecting subsequent pregnancies), and measurement error did not unduly bias my findings.

Limitations

There were also limitations of my research that need to be considered when interpreting the findings. First, while I conducted sensitivity analyses to test for measurement error, I cannot be certain that measurement error did not occur as a result of mothers mis-reporting medication use, not taking prescribed medications, or using medications that were not prescribed to them. Second, I did not evaluate associations with specific medications, though different medications within the same class can have different mechanisms of action. For example, different antidepressant medications differentially act on serotonin and norepinephrine receptors.[13] Third, I did not include measures of medication dose or detailed assessment of duration of medication exposure. Fourth, while I used methods to help account for unmeasured confounding, I could not rule out all confounding. The Swedish registry data did not include in-depth assessment of several key potential confounding factors. Of particular importance, I did not adjust for diagnoses indicating medication use (e.g., diagnoses of depressive disorders and conditions causing pain) because these diagnoses in registry data may be imprecise.[14] The registry data I used only included diagnoses made by specialist. Therefore, I did not captured diagnoses made by primary care doctors and individuals who did not seek treatment for their conditions. Fifth, it is plausible that the null associations I observed in models that adjusted for unmeasured

confounding was not indicative of a lack of causal effects. Random measurement error that is not shared by siblings could have led to an attenuation in sibling comparison associations.[15] A failure to find a difference among offspring born to women who were prescribed medications before pregnancy only and offspring born to women who were prescribed medications during pregnancy may have been due to both maternal medication use before and during pregnancy having effects on fetal development. Similarly, it is plausible that null associations observed in active comparator designs were due to both the medication under study and the active comparator having causal effects. Sixth, I conducted all analyses using data obtained from Sweden, and I do not know if my findings will generalize to countries outside of Sweden given between-country differences (e.g., higher prescribing rates in the US compared to Sweden).[16,17] However, in theory, these differences should not impact the ability to detect a causal effect of medication exposure. Seventh, there are several important outcomes that I did not study. Therefore, I cannot make conclusions about the overall safety of using the medications during pregnancy across numerous domains.

Clinical implications

Despite the limitations of my research, I believe my findings have important clinical implications. First, the findings could provide reassurance to women considering antidepressant and POA use during pregnancy. The results suggested the majority of the observed associations between exposure to the medications and the adverse outcomes are due to confounding factors, indicating that intrauterine exposure to antidepressants is unlikely to have substantial causal effects on increasing the risk PTB, SGA, ASD, and ADHD, and intrauterine exposure to POAs is unlikely to have substantial causal effects on increasing the risk of PTB and SGA. Moreover, the results showed that the absolute risks of the assessed outcomes were low following intrauterine

exposure to antidepressants and POAs. In other words, the vast majority of exposed offspring did not have the outcomes (Table V.1). From a clinical decision-making standpoint, it is important to interpret absolute risks in the context of weighing the potential benefits from the medication with the potential risk and impact of the adverse outcome. For example, a small increase risk in preterm birth or small for gestational age may be tolerable when considering the risk of untreated maternal depression.

Second, because my results suggested the majority of the observed associations were due to background factors that differ between exposed and unexposed women rather than exposure to the medications themselves, my findings highlight the need to screen pregnant women and women of childbearing age. This is consistent with recommendations from major organizations, including the US Preventive Services Task Force, for medical practitioners to routinely screen all adults, including pregnant women, for mental health problems.[18] Recent advances in computer adaptive testing and remote assessments may help expedite the screening of mental health problems in perinatal women.[19-22] Based on the information gathered from screenings, medical practitioners should collaboratively discuss treatments options with their patients to decide if treatment should include medication, psychotherapy (e.g., cognitive behavioral therapy or interpersonal therapy for depression[23] or cognitive behavioral therapy for pain management)[24] or a combination of both. Medical practitioners should also communicate information gathered from screenings to other providers involved in patient care in an effort to coordinate care. Additionally, medical practitioners should encourage at-risk women to engage in self-care activities (e.g., exercise) and seek social support to help reduce stressors.

Third, given that my findings could not rule out small independent associations with adverse birth outcomes, particularly PTB, it may be prudent for women prescribed

antidepressants and POAs during pregnancy to consider other precautions that may reduce the risk of PTB, such as reducing stress, preventing tobacco exposure, progesterone supplements, folate supplements, omega-3 long-chain polyunsaturated fatty acid supplements, and antibiotic treatment of intra-uterine infections.[25]

Future research directions

In order to continue to improve clinical care, there are several crucial future directions for research on psychiatric medication use during pregnancy. First, studies need to explore finer-grained exposures that consider the type of medication, the duration and dosage of the mediation, and the timing of the exposure during pregnancy. Second, future research needs to test the consequences of prenatal exposure to antidepressants and POA on other important developmental outcomes. The research on POA exposure and longer-term outcomes (e.g., ASD and ADHD) is particularly lacking, as is the research evaluating consequences of combination use of the medications. Third, because confounding factors appear to largely be responsible for observed associations, future studies should evaluate what specific factors other than exposure to the mediations may be responsible for the increased occurrence of adverse outcomes among exposed offspring. Based on previous research possible factors that could account for associations with prenatal antidepressants exposure include maternal depression and stress,[26,27] genetic influences,[28-30] and poor health practices during pregnancy.[31] Possible factors that could account for associations with prenatal POA exposure include conditions that cause pain (e.g., traumatic injury, acute or chronic inflammation, or musculoskeletal disorders) and co-occurring mental health problems.[32-38] Fourth, research should evaluate whether confounding factors could explain the small independent associations I observed with adverse birth outcomes after accounting for both measured and unmeasured confounding. This would require in-depth

assessments of confounding factors. Fifth, studies should also explore causal mechanisms that could explain a small increased risk of adverse birth outcomes. Rodent studies may be particularly well suited to study causal mechanisms as they can use random assignment. Sixth, my research along with other studies and meta-analyses that also did not find support for independent associations between maternal antidepressant use during pregnancy and ASD and ADHD[1-8] suggest that rodent experiments should not search for causal mechanisms for effects of prenatal antidepressant exposure on symptoms of ASD ADHD as these mechanisms are unlikely to exist.

Conclusions

In conclusion, my dissertation research comprised three studies that examined the effects of antidepressant and analgesic medications during pregnancy. Specifically, I evaluated whether prenatal exposure to antidepressant medications increase the risk of two adverse birth outcomes – PTB an SGA – and two neurodevelopmental problems – ASD and ADHD and whether prenatal exposure to POA medications increase the risk of PTB and SGA. My results showed that the absolute risks of the outcomes were low following exposure to the medications. Furthermore, my results did not support large causal effects as they suggested that observed associations between prenatal exposure to the mediations and the outcomes were largely due to background factors that differed between exposed and unexposed offspring. These results have important translational implications for clinical care and subsequent basic science exploring the risks and benefits of these medications.

Table V.1. Percent of offspring who did not have the adverse outcome

Exposed	Not PTB	Not SGA	No ASD by 15 years	No ADHD 15 years
Antidepressants	93%	97%	95%	87%
Opioid analgesics	94%	98%	--	--
Both medications	92%	97%	--	--

PTB=preterm birth. SGA=small for gestational age. ASD=autism spectrum disorder. ADHD=attention-deficit/hyperactivity disorder.

References

1. Kobayashi T, Matsuyama T, Takeuchi M, Ito S. Autism spectrum disorder and prenatal exposure to selective serotonin reuptake inhibitors: A systematic review and meta-analysis. *Reproductive Toxicology.* 2016;65:170-178.
2. 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-British Medical Journal.* 2017;357.
3. 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 : an international journal of obstetrics and gynaecology.* 2017.
4. Man KK, 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. *Neuroscience & Biobehavioral Reviews.* 2018;86:1-11.
5. Morales DR, Slattery J, Evans S, Kurz X. Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: systematic review of observational studies and methodological considerations. *BMC medicine.* 2018;16(1):6.
6. Kaplan YC, Keskin-Arslan E, Acar S, Sozmen K. Maternal SSRI discontinuation, use, psychiatric disorder and the risk of autism in children: a meta-analysis of cohort studies. *British journal of clinical pharmacology.* 2017;83(12):2798-2806.
7. Mezzacappa A, Lasica PA, Gianfagna F, et al. Risk for Autism Spectrum Disorders According to Period of Prenatal Antidepressant Exposure: A Systematic Review and Meta-analysis. *JAMA Pediatr.* 2017;171(6):555-563.

8. Zhou X-H, Li Y-J, Ou J-J, Li Y-M. Association between maternal antidepressant use during pregnancy and autism spectrum disorder: an updated meta-analysis. *Molecular autism.* 2018;9(1):21.

9. Cantarutti A, Merlino L, Giaquinto C, Corrao G. Use of antidepressant medication in pregnancy and adverse neonatal outcomes: A population-based investigation. *Pharmacoepidemiology and Drug Safety.* 2017:n/a-n/a.

10. Yazdy MM, Desai RJ, Brogly SB. Prescription Opioids in Pregnancy and Birth Outcomes: A Review of the Literature. *J Pediatr Genet.* 2015;4(2):56-70.

11. O'Connor AB, O'Brien L, Alto WA, Wong J. Does concurrent in utero exposure to buprenorphine and antidepressant medications influence the course of neonatal abstinence syndrome? *Journal of Maternal-Fetal & Neonatal Medicine.* 2016;29(1):112-114.

12. Kallen B, Reis M. Neonatal Complications After Maternal Concomitant Use of SSRI and Other Central Nervous System Active Drugs During the Second or Third Trimester of Pregnancy. *Journal of Clinical Psychopharmacology.* 2012;32(5):608-614.

13. Stahl SM. Antidepressants. In: *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications.* 4 ed. Cambridge, United Kingdom: Cambridge University Press; 2013.

14. Yonkers KA, Forray A, Smith MV. Maternal Antidepressant Use and Pregnancy Outcomes. *JAMA.* 2017;318(7):665-666.

15. Frisell T, Oberg AS, Kuja-Halkola R, Sjolander A. Sibling comparison designs: Bias from non-shared confounders and measurement error. *Epidemiology.* 2012;23:713-720.

16. Bateman BT, Hernandez-Diaz S, Rathmell JP, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. *Anesthesiology.* 2014;120(5):1216-1224.

17. Handal M, Engeland A, Ronning M, Skurtveit S, Furu K. Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: a population-based cohort study. *European Journal of Clinical Pharmacology.* 2011;67(9):953-960.

18. Siu AL, Bibbins-Domingo K, Grossman DC, et al. Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2016;315(4):380-387.

19. Gibbons RD, Weiss DJ, Frank E, Kupfer D. Computerized Adaptive Diagnosis and Testing of Mental Health Disorders. In: Cannon TD, Widiger T, eds. *Annual Review of Clinical Psychology, Vol 12.* Vol 12. Palo Alto: Annual Reviews; 2016:83-104.

20. Gibbons RD, Weiss DJ, Pilkonis PA, et al. Development of a computerized adaptive test for depression. *Archives of General Psychiatry.* 2012;69(11):1104-1112.

21. Gibbons RD, Weiss DJ, Pilkonis PA, et al. Development of the CAT-ANX: A Computerized Adaptive Test for Anxiety. *American Journal of Psychiatry.* 2014;171(2):187-194.

22. La Porte LM, Kim JJ, Adams MG, Zagorsky BM, Gibbons R, Silver RK. Feasibility of perinatal mood screening and text messaging on patients' personal smartphones. *Arch Womens Ment Health.* 2019.

23. van Ravesteyn LM, Lambregtse-van den Berg MP, Hoogendijk WJ, Kamperman AM. Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment meta-analysis. *PLoS ONE.* 2017;12(3).

24. van Tulder MW, Ostelo R, Vlaeyen JWS, Linton SJ, Morley÷ SJ, Assendelft WJJ. Behavioral Treatment for Chronic Low Back Pain: A Systematic Review Within the Framework of the Cochrane Back Review Group. *Spine.* 2000;25(20):2688-2699.

25. Newnham JP, Dickinson JE, Hart RJ, Pennell CE, Arrese CA, Keelan JA. Strategies to prevent preterm birth. *Front Immunol.* 2014;5:584-584.

26. Jarde A, Morais M, Kingston D, et al. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: A systematic review and meta-analysis. *JAMA Psychiatry.* 2016;73(8):826-837.

27. Talge NM, Neal C, Glover V. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *Journal of Child Psychology and Psychiatry.* 2007;48(3-4):245-261.

28. Lichtenstein P, Carlstrom E, Rastam M, Gillberg C, Anckarsater H. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am J Psychiatry.* 2010;167(11):1357-1363.

29. Scherff A, Taylor M, Eley TC, Happe F, Charman T, Ronald A. What causes internalising traits and autistic traits to co-occur in adolescence? A community-based twin study. *J Abnorm Child Psychol.* 2014;42(4):601-610.

30. Cole J, Ball HA, Martin NC, Scourfield J, McGuffin P. Genetic overlap between measures of hyperactivity/inattention and mood in children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 2009;48(11):1094-1101.

31. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *General Hospital Psychiatry.* 2009;31(5):403-413.

32. Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics.* 2015;135(5):842-850.

33. Quinn PD, Hur K, Chang Z, et al. Incident and long-term opioid therapy among patients with psychiatric conditions and medications: A national study of commercial health care claims. *Pain.* 2017;158(1):140-148.

34. Gustavsson A, Bjorkman J, Ljungcrantz C, et al. Pharmaceutical treatment patterns for patients with a diagnosis related to chronic pain initiating a slow-release strong opioid treatment in Sweden. *Pain.* 2012;153(12):2325-2331.

35. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: Retrospective analysis. *BMJ.* 2017;356:j760.

36. Fredheim OMS, Borchgrevink PC, Mahic M, Skurtveit S. A pharmacoepidemiological cohort study of subjects starting strong opioids for nonmalignant pain: A study from the Norwegian Prescription Database. *Pain.* 2013;154(11):2487-2493.

37. Larochelle MR, Zhang F, Ross-Degnan D, Wharam JF. Trends in opioid prescribing and co-prescribing of sedative hypnotics for acute and chronic musculoskeletal pain: 2001–2010. *Pharmacoepidemiology and Drug Safety.* 2015;24(8):885-892.

38. Kobus AM, Smith DH, Morasco BJ, et al. Correlates of higher-dose opioid medication use for low back pain in primary care. *Journal of Pain.* 2012;13(11):1131-1138.

Curriculum Vitae

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EDUCATION

Indiana University - Bloomington, Bloomington, IN
PhD, Psychology, July 2021
Thesis: *Maternal use of psychiatric medications during pregnancy and adverse birth outcomes and neurodevelopmental problems in children*
Advisor: Brian M. D'Onofrio, PhD

Cornell University, Ithaca, NY
MA Human Development, August 2014
Thesis: *Using multiple statistical methods to assess how maternal sociodemographic risk factors can be used to effectively target families for home visiting programs*
Advisor: John Eckenrode, PhD

Tulane University, New Orleans, LA
B.S., *summa cum laude*, May 2012
Major in Psychology with departmental honors
Major in Studio Art
Minor in Art History
Thesis: *Being correct or being creative: The effect of feedback and task type on measures of well-being and motivation*
Advisor: Carrie L. Wyland, PhD

HONORS AND AWARDS

2020	J.R. Kantor Graduate Award for distinction in research, Indiana University
2019	Travel award for the MONA Perinatal Mental Health Conference
2012	Phi Beta Kappa, Tulane University
2012	Mortar Board, Tulane University
2012	Anne M. McPherson Undergraduate Research Award, Tulane University
2011	Honorable Mention Community Involvement Award, Tulane University
Fall 2008-Spring 2012	Dean's List, Tulane University
Fall 2008-Spring 2012	Presidential Scholar Award, Tulane University

GRANT FUNDING

2016 **National Institute of Mental Health funded T32 Clinical Research Training Grant (T32MH103213)**
Title: Exploring the consequences of in-utero exposure to prescription medications
Funding: Two years funding for graduate stipend and tuition

2015 **National Science Foundation Graduate Research Fellowship (1342962)**
Title: Testing the causal effects of fetal growth and inter-pregnancy interval on child development.
Funding: Three years funding for graduate stipend and tuition

ADDITIONAL GRANT EXPERIENCE – *Assisted in developing and writing these grants.*

2019 **National Institute on Drug Abuse (R01DA048042)**
Title: Maternal use of prescribed opioid analgesics and risk of adverse offspring outcomes
Primary Investigators: Brian M. D'Onofrio, PhD & A. Sara Oberg, PhD, MD
Funding: Three years of funding, $1,220,000

2019 **Swedish Research Council (2018-02679)**
Title: Prescribed Opioid Analgesic Use during Pregnancy and Risk for Adverse Birth Outcomes and Neurodevelopmental Problems in Offspring
Primary Investigator: Brian M. D'Onofrio, PhD
Funding: Three years of funding, $400,000

PUBLICATIONS

1. Lin, L., **Sujan, A.C.**, Butwicka, A., Chang, Z., Cortese, S., Quinn, P.D., Viktorin, A., Oberg, A.S., D'Onofrio, B.M., Larsson, H. (in press). Associations of prescribed ADHD medication in pregnancy with pregnancy-related and offspring outcomes: A systematic-review of current Evidence and a roadmap for future research. *CNS Drugs.*

2. **Sujan, A.C.**, Oberg, A.S., Quinn, P.D, & D'Onofrio, B.M. (2019*).* Annual research review: Maternal antidepressant use during pregnancy and offspring neurodevelopmental problems – a critical review and recommendations for future research. *Journal of Child Psychology and Psychiatry, 60*(4):356-376*.* doi: 10.1111/jcpp.13004. PMCID: PMC6438736.

3. **Sujan, A.C.**, Quinn, P.D., Rickert, M.E., Wiggs, K.K., Lichtenstein, P., Larsson, H., Almqvist, C, Oberg, A.S., D'Onofrio, B.M. (2019). Maternal prescribed opioid analgesic use during pregnancy and associations with adverse birth outcomes: A population-based study. *PLOS Medicine, 16(12): e1002980.* doi: 10.1371/journal.pmed.1002980. PMID: 31790390.

4. **Sujan, A.C.**, Rickert, M.E., Class, Q.A., Van Hulle, C., & D'Onofrio, B.M. (2019). Predictors and child outcomes associated with short and long interpregnancy intervals. *Early Child Development and Care, 1-12.* doi:10.1080/03004430.2019.1703111.

5. Class, Q.A., Rickert, M.E., Larsson, H., Oberg, A.S., **Sujan, A.C,** Almqvist, C., Lichtenstein, P., & D'Onofrio, B.M., (2018). Outcome-dependent associations between short interpregnancy interval and offspring psychological and educational problems: A population-based quasi-experimental study. *International Journal of Epidemiology*, *47*(4):1159-1168. doi: 10.1093/ije/dyy042. PMCID: PMC6124608.

6. **Sujan, A.C**., Oberg, A.S., & D'Onofrio, B.M. (2018*).* Understanding antidepressant use during pregnancy. *Pediatrics for Parents*.

7. Class, Q.A., Rickert, M.E., Oberg, A.S., **Sujan, A.C.**, Almqvist, C., Larsson, H., Lichtenstein, P., & D'Onofrio, B.M., (2017). Within-family analysis of interpregnancy interval and adverse birth outcomes. *Obstetrics and Gynecology, 130*(6), 1304-1311. doi:10.1097/AOG.0000000000002358. PMCID: PMC5783305.

8. D'Onofrio, B.M. & **Sujan, A.C.** (2017). Pregnancy Exposure Studies Need to Consider Substance Use—Reply. *Journal of the American Medical Association, 318*(7), 666-667. doi:10.1001/jama.2017.9194. PMCID: PMC419718.

9. **Sujan, A.C.** & Eckenrode, J. (2017). An illustration of how program implementers can use population-specific analyses to facilitate the selection of evidence-based home visiting programs. *Psychosocial Interventions, 26*(2), 117-124. doi:10.1016/j.psi.2017.01.001.

10. **Sujan, A.C**., Rickert, M.E., Oberg, A.S., Quinn, P.D., Hernandez-Diaz, S., Almqvist, C., Lichtenstein, P., Larsson, H., & D'Onofrio, B.M. (2017*).* 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. *Journal of the American Medical Association, 317*(15), 1553-1562. doi:10.1001/jama.2017.3413. PMCID: PMC5875187.

11. D'Onofrio, B.M., Class, Q.A., Rickert, M.E., **Sujan, A.C.**, Larsson, H., Kuja-Halkola, R., Sjölander, A., Almqvist, C., Lichtenstein, P., Oberg, A.S. (2016). Translational epidemiologic approaches to understanding the consequences of early-life exposures. *Behavior Genetics. 46(3), 315-328*. doi: 10.1007/s10519-015-9769-8. PMCID: PMC4860044.

12. **Sujan, A.C.**, Rickert, M.E., Class, Q.A., Coyne, C.A., Lichtenstein, P., Almqvist, C., Larsson, H., Sjölander, A., Lahey, B.B., Van Hulle, C., Waldman, I., Oberg, S.A. & D'Onofrio, B.M. (2016). A genetically informed study of the associations between maternal age at childbearing and adverse perinatal outcomes. *Behavior Genetics, 46(3), 431-456*. doi:10.1007/s10519-015-9748-0. PMCID: PMC4808498.

13. **Sujan, A. C.**, Humphreys, K. L., Ray, L. A., & Lee, S. S. (2014). Differential association of child abuse with self-reported versus laboratory-based impulsivity and risk-taking in young adulthood. *Child Maltreatment, 19*(3-4), 145-155. doi:10.1177/1077559514543827.

14. Miron, D., **Sujan, A.**, & Middleton, M. (2013). Considering the best interests of infants in foster care placed separately from their siblings. *Children and Youth Services Review, 35*(9), 1385–1392. doi:10.1016/j.childyouth.2013.05.008

MANUSCRIPTS UNDER REVIEW

1. Quinn, P.D., Fine, K.L., Rickert, M.E., **Sujan, A.C.**, Boersma, K., Chang, Z., Franck, J., Lichtenstein, P., Larsson, H., & D'Onofrio, B.M. (invited resubmission). Prescribed opioid initiation and substance use problems in young people: A nationwide Swedish study. *JAMA Pediatrics.*

2. **Sujan, A.C.**, Rickert, M.E., Quinn, P.D., Ludema, C., Wiggs, K.K., Lichtenstein, P., Larsson, H., Oberg, A.S., D'Onofrio, B.M. (under review). *A Population-based study of concurrent prescriptions of opioid analgesic and selective-serotonin reuptake inhibitor medications during pregnancy and risk for adverse birth outcomes.*

3. Wiggs, K.K., Rickert, M.E., **Sujan, A.C.**, Quinn, P.D., Lichtenstein, P., Larsson, H., Oberg, A.S., D'Onofrio, B.M. (invited resubmission). The association between maternal antiepileptic drug use during pregnancy and offspring ADHD. *Neurology.*

MANUSCRIPTS IN PREPARATION

1. Fine, K.L., Rickert, M.E., O'Reilly, L.M., **Sujan, A.C**., Boersma, K., Chang, Z., Franck, J., Lichtenstein, P., Larsson, H., D'Onofrio, B.M., & Quinn, P.D. (in preparation). *Association of early prescription opioid initiation with risk of suicidal behavior and depression.*

2. †O'Reilly, L., †**Sujan, A.C.**, Rickert, M.E., Vaughan, E.B., Larsson, H., Lichtenstein, P., D'Onofrio, B.M. (in preparation). *The association between maternal age at childbearing and morbidity and mortality in offspring*. (†indicates equal authorship)

3. **Sujan, A.C.**, Quinn, P.D., Rickert, M.E., Wiggs, K.K., Lichtenstein, P., Larsson, H., Oberg, A.S., D'Onofrio, B.M. (in preparation). *A nation-wide Swedish study of opioid analgesic prescribing patterns during pregnancy and associated pre-existing mental health conditions.*

ORAL PRESENTATIONS

1. **Sujan, A.C.**, Rickert, M.E., Quinn, P.D., Ludema, C., Wiggs, K.K., Lichtenstein, P., Larsson, H., Oberg, A.S., D'Onofrio, B.M. (2020, October). *Concurrent prescriptions of opioid analgesic and selective-serotonin reuptake inhibitor medications during pregnancy and risk for adverse birth outcomes.* Paper to be presented at the 48th International Marce Society for Perinatal Mental Health, Iowa City, Iowa, USA.

2. Fine, K.L., Rickert, M.E., O'Reilly, L.M., **Sujan, A.C.,** Boersma, K., Chang, Z., Franck, J., Lichtenstein, P., Larsson, H., D'Onofrio, B.M., & Quinn, P.D. (2020, April) *Association of early prescription opioid initiation with risk of suicidal behavior and depression.* The 2020 Collaborative Perspectives on Addiction Annual Meeting, San Diego, CA, USA. (Conference cancelled).

3. Quinn, P.D., Fine, K.L., Rickert, M.E., **Sujan, A.C.,** Boersma, K., Chang, Z., Franck, J., Lichtenstein, P., Larsson, H., & D'Onofrio, B.M. (2020, April) *Prescribed opioid initiation and substance use problems in young people: A nationwide Swedish study.* The 2020 Collaborative Perspectives on Addiction Annual Meeting, San Diego, CA, USA. (Conference cancelled).

4. **Sujan, A.C.**, Quinn, P.D., Rickert, M.E., Wiggs, K.K., Lichtenstein, P., Larsson, H., Oberg, A.S., D'Onofrio, B.M. (2019, October). *Maternal prescribed opioid analgesic use during pregnancy and risk for adverse birth outcomes in offspring: A population-based study*. Paper presented at The Marcé of North America: 4th Biennial Conference on Perinatal Mental Health, University of North Carolina, Chapel Hill, NC, USA.

5. O'Reilly, L.M., **Sujan, A.C.**, Rickert, M.E., Vaughan, E., Larsson, H., Lichtenstein, P., & D'Onfroio, B.M. (2019, October). *The association between maternal age at childbearing and suicidal behavior using Swedish, population-based registers.* Paper presented at the International Summit of Suicide Research, Miami, FL, USA.

6. **Sujan, A.C.**, Quinn, P.D., Rickert, M.E., Wiggs, K.K., Lichtenstein, P., Larsson, H., Oberg, A.S., D'Onofrio, B.M. (2018, October). *Maternal opioid analgesic use during pregnancy and adverse birth outcomes*. Paper presented at The Society for Research and Child Development Conference on the Use of Secondary and Open Source Data in Developmental Science, Phoenix, AZ, USA.

7. **Sujan, A.C.**, Quinn, P.D., Rickert, M.E, Wiggs, K.W., Lichtenstein, P., Larsson, H., Oberg, A.S., & D'Onofrio, B.M. (2018, June). *Maternal prescribed opioid analgesic use during pregnancy and offspring neurodevelopmental problems.* Paper presented at The Behavior Genetics Association Meeting, Boston, MA, USA.

8. **Sujan, A.C.** (2018, April). *Prescribed opioid analgesic use during pregnancy: Research proposal & preliminary findings*. Presented at Clinical Colloquium, Indiana University – Bloomington, Bloomington, IN, USA.

9. **Sujan, A.C.**, Rickert, M.E., Oberg, A.S., Quinn, P.D., Hernandez-Diaz, S., Almqvist, C., Lichtenstein, P., Larsson, H., & D'Onofrio, B.M. (2017, June). *Maternal antidepressant use during the first trimester of pregnancy and offspring neurodevelopmental problems.* Paper presented at The Behavior Genetics Association Meeting, Oslo, Norway.

10. **Sujan, A.C.**, Rickert, M.E., Oberg, A.S., Hernandez-Diaz, S., Almqvist, C., Lichtenstein, P., Larsson, H., & D'Onofrio, B.M. (2017, April). *A family-based study on the associations between maternal SSRI use during pregnancy and offspring birth outcomes.* Paper presented at the meeting of the Society for Research and Child Development, Austin, TX, USA.

11. **Sujan, A.C.**, Rickert, M.E., Oberg, A.S., Hernandez-Diaz, S., Almqvist, C., Lichtenstein, P., Larsson, H., & D'Onofrio, B.M. (2016, December*). Antidepressant use during the first trimester of pregnancy and offspring neurodevelopmental problems.* Paper presented at Clinical Colloquium, Indiana University – Bloomington, Bloomington, IN, USA

12. Hoyniak, C., **Sujan, A.C.**, McQuillan, M., Bates, J.E. (2016, September). *Parent behavior training case presentation: Family routines study pilot case.* Case presented at Clinical Colloquium, Indiana University – Bloomington, Bloomington, IN, USA.

13. Vaughan, E.B., **Sujan, A.C.**, Rickert, M., Van Hulle, C.A., Lahey, B.B., D'Onofrio, B.M. (2016, May). *Mother's age at childbearing and offspring internalizing problems*. Paper presented at the Society for Research on Adolescence Biennial Meeting. Baltimore, MD, USA.

14. **Sujan, A.C.**, Rickert, M.E., Class, Q.A., Coyne, C.A., Lichtenstein, P., Almqvist, C., Larsson, H., Sjölander, A., Lahey, B.B., van Hulle, C., Waldman, I., Oberg, S.A. & D'Onofrio, B.M. (2015, June). *A genetically informed study of the associations between maternal age at childbearing and adverse perinatal outcomes.* Paper presented at The Behavior Genetics Association Meeting, San Diego, CA, USA.

15. **Sujan, A.C.**, Rickert, M.E., Class, Q.A., Coyne, C.A., Lichtenstein, P., Almqvist, C., Larsson, H., Sjölander, A., Lahey, B.B., van Hulle, C., Waldman, I., Oberg, S.A. & D'Onofrio, B.M. (2015, March). *A genetically informed study of the associations between maternal age at childbearing and adverse perinatal outcomes.* Paper presented at Developmental Seminar, Indiana University – Bloomington, Bloomington, IN, USA.

16. Miron, D., **Sujan, A.C.**, & Middleton, M. (2013, April). *Considering the best interests of infants in foster care placed separately from their siblings.* Paper presented at Child Psychiatry Grand Rounds, Tulane University School of Medicine, New Orleans, LA, USA.

POSTER PRESENTATIONS

1. Wiggs, K.K., Rickert, M.E., **Sujan, A.C.**, Quinn, P.D., Lichtenstein, P., Larsson, H., Oberg, A.S., D'Onofrio, B.M. (2019, January). *The association between maternal antiepileptic drug use during pregnancy and offspring ADHD.* Poster presented at American Professional Society for ADHD and Related Disorders, Washington, DC, USA.

2. Wiggs, K.K., Rickert, M.E., **Sujan, A.C.**, Quinn, P.D., Lichtenstein, P., Larsson, H., Oberg, A.S., D'Onofrio, B.M. (2018, October). *Maternal antiepileptic drug use during pregnancy and offspring neurodevelopmental disorder.* Poster presented at The Society for Research and Child Development Conference on the Use of Secondary and Open Source Data in Developmental Science, Phoenix, AZ, USA.

3. **Sujan, A.C.**, Quinn, P.D., Rickert, M.E., Wiggs, K.K., Lichtenstein, P., Larsson, H., Oberg, A.S., D'Onofrio, B.M. (2018, September). *The critical need to consider polypharmacy when studying antidepressant exposure during pregnancy and risk for offspring psychopathology*. Poster presented at The Society for Research in Psychopathology Conference, Indianapolis, IN, USA.

4. Wiggs, K.K., Rickert, M.E., **Sujan, A.C.**, Quinn, P.D., Lichtenstein, P., Larsson, H., Oberg, A.S., D'Onofrio, B.M. (2018, September). *Examining the association between prenatal exposure to antiepileptic drugs and offspring attention-deficit hyperactivity disorder.* Poster presented at The Society for Research in Psychopathology Conference, Indianapolis, IN, USA.

5. **Sujan, A.C.**, Rickert, M.E., Class, Q.A., Coyne, C.A., Lichtenstein, P., Almqvist, C., Larsson, H., Sjölander, A., Lahey, B.B., van Hulle, C., Waldman, I., Oberg, S.A. & D'Onofrio, B.M. (2015, October). *A genetically informed study of the associations between maternal age at childbearing and adverse perinatal outcomes.* Poster presented at The Psychological and Brain Sciences Homecoming, Indiana University – Bloomington, Bloomington, IN, USA.

6. **Sujan, A.C.**, Humphreys, K. H., Ray, L. A., & Lee, S. S. (2014, April). *Differential association of child abuse with self-report versus laboratory-based risk-taking.* Poster presented at the 19th National Conference on Child Abuse and Neglect, New Orleans, LA, USA.

7. **Sujan, A.C.**, & Wyland, C. (2013, January). *Being correct or being creative: The effect of feedback and task type on measures of well-being and motivation*. Poster presented at the 14th annual convention for the Society for Personality and Social Psychology, New Orleans, LA, USA.

8. Wyland, C., **Sujan, A.C.**, & Roggeveen, S**.** (2013, January). *The relationship between use of Facebook and narcissism, empathy and perspective-taking.* Poster presented at the 14th annual convention for the Society for Personality and Social Psychology, New Orleans, LA, USA.

RESEARCH EXPERIENCE

August 2014 to present

Developmental Psychopathology Lab
Indiana University–Bloomington, Department of Psychological & Brain Sciences
Mentor: Brian M. D'Onofrio, PhD
Description: My research focuses on understanding potential consequences of prenatal exposures on risk for adverse birth outcomes and neurodevelopmental problems. I am particularly interested in understanding the consequences of women's use of psychiatric medications during pregnancy on offspring development. Because I study exposures that cannot be randomly assigned, I use large population-level datasets and advanced epidemiological methods to account for differences between exposed and unexposed offspring.

August 2013 to August 2014

Bronfenbrenner Center for Translational Research
Cornell University
Mentor: John J. Eckenrode, PhD
Description: I used data from the control group of the Nurse Family Partnership Elmira, NY randomized clinical trial to illustrate how program implementers can use community-level data and standard statistical methods to target existing home-visiting programs to the most at-risk families in their communities.

March 2013 to August 2013

Stress Impulsivity Project
University of California, Los Angeles
Mentor: Kathryn L. Humphreys, PhD, EdM
Description: We evaluated associations between stress and risk-taking and impulsivity. The stressors we assessed were (1) an acute laboratory induced stressor and (2) a self-reported history of child abuse. We measured risk-taking and impulsivity with self-report measures and laboratory behavioral tasks.

June 2013 to August 2013

Infant Development Study
Tulane University School of Medicine
Mentors: Stacy Drury, MD, PhD and Charles H. Zeanah, Jr., MD
Description: This study investigated the extent to which positive early parent-child relationships could protect children from experiencing negative effects of stress. My primary responsibility was coding mother-child attachment styles assessed with the Strange Situation Procedure.

September 2011 to January 2013 — **Attachment and Siblings in Foster Care Project**
Tulane University School of Medicine
Mentor: Devi Miron Murphy, PhD
Description: We wrote a paper making recommendations for child welfare workers to consider when making placement decisions involving tradeoffs between preserving caregiver relationships versus sibling relationships.

April 2012 to August 2013 — **Traumatology Lab**
Tulane University, School of Social Work
Mentor: Charles R. Figley, PhD
Description: We conducted mixed methods research to assess stressors and coping mechanisms in a low socioeconomic community in Louisiana exposed to multiple natural disasters.

August 2010 to May 2012 — **The Self in Social Psychology Lab**
Tulane University, School of Science and Engineering
Mentor: Carrie L. Wyland, PhD
Description: We conducted research on self-esteem, well-being, and motivation. My honors thesis was on the effects of feedback on motivation and well-being.

CLINICAL EXPERIENCE

August 2016 to December 2019 — **Indiana University Cognitive Behavioral Therapy Clinic**
Indiana University–Bloomington, Department of Psychological & Brain Sciences
Supervisor: Brittany M. Brothers, PhD, HSPP
Description: I conduct psychological assessments using the Structured Clinical Interview and self-report measures and provide cognitive behavioral therapy to treat depression, anxiety, and post-traumatic stress disorder.

August 2018 to May 2019 — **Perinatal Mood and Anxiety Disorders Clinic**
Indiana University Health Neurosciences Center, Indianapolis, IN
Supervisor: Rebecca Bottom, MD
Description: I worked with psychiatrists to treat pregnant and postpartum women with perinatal psychiatric problems. My primary role was providing brief cognitive behavior therapy interventions to target depression and anxiety.

January 2018 to June 2018 — **Mood/Anxiety Clinic**
Riley Hospital for Children, Indianapolis, IN
Supervisors: Ann Lagges, PhD and Patrick D. Quinn, PhD
Description: I provided evidence-based treatment, primarily cognitive behavioral therapy, to children and adolescents with depressive and anxiety disorders.

January 2015 to May 2018 — **Indiana University Parent-Child Clinic**
Indiana University–Bloomington, Department of Psychological & Brain Sciences
Supervisors: John E. Bates, PhD and Amy Holtzworth-Munroe, PhD
Description: I provided parent behavior training to families with young children.

September 2017 to January 2018 — **Pediatric Psychology Testing Practicum**
Riley Hospital for Children, Indianapolis, IN
Supervisor: William G. Kronenberger, PhD
Description: I administered, scored, and interpreted the following psychological tests for children and adolescents: Wechsler Intelligence Scale for Children V, Woodcock Johnson IV, Kaufman Brief Intelligence Test 2, California Verbal Learning Test for Children, Wide Range Assessment of Memory and Learning 2, Beery-Buktenica Developmental Test of Visual-Motor Integration, and Thematic Apperception Test.

June 2011 to August 2013 — **The Tulane Infant Team**
Tulane University School of Medicine
Supervisors: Charles H. Zeanah, Jr., MD and Julie Larrieu, PhD
Description: As an undergraduate student intern, I observed therapy sessions and assisted in daycare observations and home visits for young children in foster care.

SUPERVISION EXPERIENCE

January 2020 to May 2020 — **Indiana University Cognitive Behavioral Therapy Clinic**
Indiana University–Bloomington, Department of Psychological & Brain Sciences
Supervisor: Lorenzo Lorenzo-Luaces, PhD
Description: I provided peer supervision to other graduate student clinicians and received feedback on my supervision form a licensed psychologist.

August 2016 to May 2018 — **Indiana University Parent-Child Clinic**
Indiana University–Bloomington, Department of Psychological & Brain Sciences
Supervisors: John E. Bates, PhD and Amy Holtzworth-Munroe, PhD
Description: I provided peer supervision to four other graduate student clinicians and received feedback on my supervision form two licensed psychologist.

TEACHING EXPERIENCE

January 2017 to May 2017 — **Methods of Experimental Psychology (PSY P211)**
Indiana University–Bloomington, Department of Psychological & Brain Sciences
Duties: As an assistant instructor, I independently taught two laboratory sections.

January 2015 to May 2015 — **Statistical Techniques (PSY K300)**
Indiana University–Bloomington, Department of Psychological & Brain Sciences
Duties: As a teaching assistant, my primary responsibility was grading.

August 2014 to December 2014 — **Abnormal Psychology (PSY P324)**
Indiana University–Bloomington, Department of Psychological & Brain Sciences
Duties: As a teaching assistant, my primary responsibility was grading.

October 2013 to December 2013 — **The Translation of Research Evidence into Practice and Policy (HD 4170)**
Cornell University, Department of Human Development
Duties: I assisted in developing an upper level undergraduate seminar by reviewing and organizing research articles and news coverage related to translational research.

ADVANCED STATISTICAL TRAINING

August 2017 to December 2017 — **Advanced Epidemiology**
Indiana University – Bloomington, School of Public Health
Instructor: Christina Ludema, PhD
Description: This course presented concepts underlying causal theory and discussed how epidemiological methods can be understood within a causal framework.

November 2015 — **Design and Analysis of Twin and Family-Based Studies**
Karolinska Institutet, Department of Medical Epidemiology and Biostatistics
Instructors: Arvid Sjölander,PhD; Ralf Kuja-Halkola,PhD; Brian D'Onofrio,PhD
Description: This week-long workshop covered theory and practice of within-family designs, which are used to estimate causal effects from observational data.

October 2015 — **Causal Diagrams – Theory and Applications**
Indiana University–Bloomington, Department of Psychological & Brain Sciences
Instructor: Anna Sara Oberg, MD, MPH, PhD
Description: This workshop covered how to use Directed Acyclic Graphs (DAGs) to illustrate relationships between variables and identify sources of bias.

January 2015 to May 2015 — **Categorical Data Analyses**
Indiana University – Bloomington, School of Education
Instructor: Leslie Rutkowski, PhD
Description: This course was on theory and practice of categorical data analyses.

August 2014 to December 2014 — **Covariance Structure Analyses**
Indiana University – Bloomington, School of Education
Instructor: Leslie Rutkowski, PhD
Description: This course focused on structural equation modeling.

CLINICAL WORKSHOPS

April 2019 **Cognitive Behavior Therapy: From Action to Insight and Back Again**
Indiana University–Bloomington, Department of Psychological & Brain Sciences
Instructor: Steven Hollon, PhD
Description: This workshop covered core components of cognitive behavior therapy and described two complex cases.

May 2018 **Best Practices in Cognitive Behavioral Therapy for Depression**
Indianapolis Institute for Cognitive Therapy
Instructor: Christine A. Padesky, PhD
Description: This workshop emphasized strategies to manage common obstacles encountered by therapist working with clients with depression.

OTHER TRAINING

June 2013 **Strange Situation Procedure Training**
University of Minnesota, Institute of Child Development
Instructors: Alan Sroufe, PhD and Elizabeth Carlson, PhD
Description: This two-week training covered how to administer the Strange Situation Procedure and how to code for different patterns of attachment in 12- to 18-month-old infants and their caregivers.

STATISTICAL/PROGRAMMING SKILLS

Experience with SAS, STATA, R, Mplus, and SPSS.

SERVICE AND LEADERSHIP ACTIVITIES

2011 to 2012 Vice-Present, Tulane University Psi Chi & Psychology Club
2011 Head Coach, Girls on the Run

PROFESSIONAL SOCIETIES

2019 to present Marcé of North America
2018 to present Association for Psychological Science
2015 to present Behavior Genetics Association
2014 to present Society for Research in Child Development
2011 to present Psi Chi

AD HOC REVIEWER

American Journal of Perinatology
BJOG
European Child & Adolescent Psychiatry
JAMA
Journal of Psychiatric Research
Neuroscience & Biobehavioral Reviews
Paediatric and Perinatal Epidemiology

SELECTED MEDIA COVERAGE

Veleta, K. (September 26, 2019). Pain during pregnancy: IU examines impact of prescribed opioids. *Inside Indiana Business*. http://www.insideindianabusiness.com/story/41105323/pain-during-pregnancy-iu-examines-impact-of-prescribed-opioids.

Thompson, H. (April 19, 2017). Study eases concerns about antidepressants, pregnancy and autism risk. *CBS News.* https://www.cbsnews.com/news/moms-antidepressant-use-pregnancy-autism/

Park, A. (April 18, 2017). Does taking antidepressants during pregnancy cause autism? *Time.* https://time.com/4743467/antidepressants-pregnancy-autism/?xid=homepage

Wilson, P. (April 18, 2017). Is Maternal antidepressant use linked with autism? *MedPage Today.* https://www.medpagetoday.com/pediatrics/autism/64616