

2021

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Xuerong Wen

University of Rhode Island, xuerongwen@uri.edu

D. Lawal

University of Rhode Island

Nicholas Belviso

University of Rhode Island

Kelly Matson

University of Rhode Island, matson@uri.edu

Shuang Wang

University of Rhode Island

See next page for additional authors

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Citation/Publisher Attribution

Wen, X., Lawal, O.D., Belviso, N. *et al.* Association Between Prenatal Opioid Exposure and Neurodevelopmental Outcomes in Early Childhood: A Retrospective Cohort Study. *Drug Saf* (2021).

<https://doi.org/10.1007/s40264-021-01080-0>

Available at: <https://doi.org/10.1007/s40264-021-01080-0>

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Authors

Xuerong Wen, D. Lawal, Nicholas Belviso, Kelly Matson, Shuang Wang, Brian J. Quilliam, and Kimford J. Meador

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Title: Association Between Prenatal Opioid Exposure and Neurodevelopmental Outcomes in Children

Xuerong Wen¹, PhD; Oluwadolapo D. Lawal¹, MPH; Nicholas Belviso¹, PharmD; Kelly L. Matson¹, PharmD; Shuang Wang¹, MPH; Brian J. Quilliam², PhD; Kimford J. Meador,³ MD

¹: Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island, Rhode Island, USA

²: College of Health Sciences, University of Rhode Island, Rhode Island, USA

³: Department of Neurology & Neurological Sciences, Stanford University School of Medicine, California, USA

Corresponding Author:

Xuerong Wen, PhD, MPH, MS

Assistant Professor of Pharmacoepidemiology and Health Outcomes

University of Rhode Island, College of Pharmacy, Department of Pharmacy Practice

7 Greenhouse Road, Suite 265F, Kingston, RI 02881

Email: xuerongwen@uri.edu; Tel: 401-874-4547

Word of count:

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Abstract	350 words	337
Manuscript text	3000 words	2987
Figures and Tables	<= 5 tables and/or figures	3 tables and 1 figure

KEY POINTS

Question. To evaluate the relationship between maternal prescription opioid use and incidence of neurodevelopmental disorders in children.

Findings. In this retrospective cohort study, 7.6% of eligible children were exposed to prescription opioids during pregnancy. We observed no overall association between maternal prescription opioid use and the risk of neurodevelopmental disorders in children. However, significantly increased risks were observed in children with longer-term opioid exposure or high cumulative doses.

Meaning. These findings suggest the need for a careful consideration of the benefits of opioid therapy during pregnancy versus potential risks of long-term neurodevelopmental disorders in children.

ABSTRACT

Importance. Little is known regarding long-term effects of fetal opioid exposure on the neurodevelopment of children.

Objective. To quantify the association between prenatal opioid exposure from maternal prescription use and long-term neurodevelopmental outcomes in children.

Design. Retrospective cohort study using administrative claims submitted to a large commercial insurance database.

Setting and Participants. We included pregnant women aged 12 – 55 years and their live-birth infants born from 2010 to 2012 present in Optum’s deidentified Clinformatics® Data Mart Database. Infants born to eligible mothers were followed till occurrence of primary outcome, loss to follow-up, or study end (December 31, 2017), whichever came first.

Exposures. Infants were considered exposed if their mothers filled ≥ 1 opioid prescription during pregnancy.

Main outcomes and measures. The primary outcome was neurodevelopmental disorders; a composite of developmental disorders, intellectual disabilities, and other relevant mental disorders in children.

Propensity score by fine-stratification was applied to adjust for confounding. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated with Cox proportional hazard models. Sensitivity analyses were conducted to examine the effects of maternal opioid use by cumulative exposure dichotomized as short-term (<14 days), by long-term use (≥ 14 days), cumulative dose (low dose: < 37.5 MME or high dose: ≥ 37.5 MME), and by trimesters.

Results. We included 24,731 mothers and their 24,912 live-born children of whom 7.6% (1,899) were exposed to prescription opioids during pregnancy. Overall, 2,138 children were diagnosed with neurodevelopmental disorders, with incidence rates of 42.0 per 1000 person-years in exposed children vs. 34.7 per 1000 person-years in unexposed children. Following adjustment for confounding, there was

no overall association between fetal opioid exposure and risks of neurodevelopmental disorders (HR: 1.16 [0.99, 1.34]). However, significantly increased risks were observed in children with longer cumulative duration of fetal opioid exposure (adjusted HR: 1.59 [1.03, 2.45]) or high cumulative doses (adjusted HR: 1.25 [1.01, 1.55]).

Conclusion and Relevance. We observed an increased risk of children neurodevelopmental disorders in women taking opioid for longer duration and at higher doses during pregnancy. Additional studies are needed to confirm these findings.

INTRODUCTION

Pain syndromes are common during pregnancy.^{1,2} Maternal opioid use has steadily increased in the past decade, with one in every five pregnant woman estimated to receive opioids during pregnancy.^{3,4} Maternal use of opioids has been associated with several negative maternal and fetal outcomes including altered fetal growth and congenital malformations.⁵⁻¹⁰ Birth defects have been associated with cognitive impairments and lower academic performance in childhood.^{11,12} Similar findings have also been reported in animal studies where exposure of rodents to opioids during critical developmental periods induced neuronal apoptosis,¹³⁻¹⁵ and was associated with structural and functional alterations.¹⁶ Little is known about the effects of maternal prescription opioid use on the neurodevelopmental outcomes of children. So far, knowledge of the potential long-term effects of fetal opioid exposure have been primarily aggregated from studies investigating cognitive impairment in relationship with birth defects^{11,12} or small sample sizes conducted in women with opioid use disorders (OUD) or illicit drug use during pregnancy (eTable 1 in the Supplement).¹⁷⁻²¹ These findings are however not generalizable to offspring of mothers receiving prescribed opioids because women with OUD or a history of illicit drug use are more likely to have higher incidence of comorbid conditions; higher likelihood of smoking, cocaine, alcohol or other drug use; or socioeconomic factors that can markedly increase the risk of neurodevelopmental disorders in the developing fetus.^{19,21,22} Moreover, it is unknown whether the potential effects of opioids on neurodevelopment differs by trimester, cumulative dose, or duration of use. Therefore, we conducted a population-based study to quantify the association of gestational prescription opioid exposure on long-term neurodevelopmental outcomes in children.

METHODS

Data Source

This study was conducted using administrative claims from January 1, 2010 to December 31, 2017 to Optum's deidentified Clinformatics® Data Mart Database; a large Commercial and Medicare Advantage

claims database.²³ This study was approved by the institutional review board of University of Rhode Island. Information on the algorithm for identifying deliveries, mother-infant linkage, estimation of date of birth and validation results using linked Rhode Island Medicaid data, opioid utilization after pregnancy, and timing of prenatal test screening is available in the supplementary method.

Pregnancy Window

The pregnancy window was defined by the estimated delivery date and last menstrual period (LMP). The LMP was calculated by subtracting 35 weeks for preterm births (identified using ICD-9 diagnosis codes: 644.0, 644.2, and 765.x), and 39 weeks for full-term births from estimated delivery date.²⁴

Inclusion/Exclusion Criteria

The study cohort comprised of mothers aged 12 to 55 years and their liveborn infants born between study start and December 31, 2012. Mothers were required to have continuous insurance eligibility 3 months prior to the estimated LMP to one month following live birth. We excluded mothers with diagnosis of cancer or OUD during baseline or pregnancy;^{25,26} women exposed to confirmed teratogenic medication during pregnancy; and women or infants with ≥ 1 inpatient or ≥ 2 outpatient claims indicating chromosomal abnormality during pregnancy or one month after live-birth. The study cohort selection diagram and operational definitions for the various exclusion criteria are presented in Figure 1 and eTable2 respectively.

Opioid Exposure

Prescription opioids in our analysis included single or combination products of hydrocodone, oxycodone, codeine, fentanyl, hydromorphone, meperidine, methadone, oxymorphone, dihydrocodeine, tapentadol, levorphanol, tramadol, transdermal buprenorphine, pentazocine, or morphine. To allow meaningful comparisons between different opioid medications, opioid doses were converted to morphine milligram equivalents (MMEs) using opioid-conversion tables.²⁷

Infants were considered exposed if their mother filled ≥ 1 opioid prescription during pregnancy and unexposed if their mothers did not fill a prescription of eligible opioids anytime during the baseline and pregnancy period. We additionally required no filling of opioid prescriptions during the baseline period in the reference group to prevent exposure misclassification arising from women who may still have opioids remaining from an earlier prescription, but available at the start of pregnancy. As such, mothers who filled opioids during baseline, but not during pregnancy were excluded.

Outcome Assessment

The primary endpoint was a composite of relevant mental disorders (henceforth regarded as neurodevelopmental disorders) in the infant, based on categories listed in Halloran et al.²⁸ To facilitate comparison with previous research, developmental disorders - a subcategory of the primary outcome - was analyzed as a secondary outcome. The primary and secondary outcomes were assessed on the basis of the presence of ≥ 1 inpatient or outpatient ICD-9 or ICD-10 diagnosis in children claims (eTable 3 in the Supplement). Following delivery, live-birth infants born to eligible mothers before December 31, 2012 (inclusive) were then followed until first diagnosis of neurodevelopmental disorders, lost to follow-up, or December 31, 2017 (the study end date), whichever came first.

Covariates

We considered known and suspected risk factors, and their proxies for adjustment in our analyses. The covariates taken into consideration were grouped as maternal sociodemographic characteristics, maternal comorbidities and mental health diagnoses, concomitant drug use, and measures of burden of illnesses such as the Obstetric Morbidity Index.²⁹ A complete list of the covariates and the time of assessment is available in eTable4.

Statistical Analysis

Cox proportional-hazard models were used to estimate the absolute rates (per 1000 person years) and hazards ratio (HR) with their 95% confidence intervals. Analyses of Schoenfeld residuals showed no

violations of the proportional hazards assumption.³⁰ In the adjusted analyses, we accounted for potential confounding by creating 50 equally sized propensity score (PS) strata based on the PS distribution among the opioid exposed women, and then weighted the untreated group in the final outcome model using the distribution of the exposed group.³¹ Following covariate adjustment, the maximum allowed standardized difference between the treatment groups was 0.1. Considering that we included mothers with multiple pregnancies, we accounted for correlation between siblings by using the Huber sandwich estimator for correction of standard errors.³² All analyses were conducted using SAS 9.4 (SAS Institute Inc).

Secondary analysis

Teratogens are often dose-dependent; therefore, we evaluated for the presence of a dose-response relationship between fetal opioid exposure and the risk of neurodevelopmental disorders using two approaches. First, exposed infants were dichotomized by median cumulative opioid dose (in MME) into low and high cumulative dose (<37.5 and \geq 37.5 MME respectively) and compared with unexposed infants. Second, we assessed the relationship between duration of exposure – dichotomized by cumulated days' supply into “short-term” (<14 days) and “long-term exposure” (\geq 14 days) - and the incidence of neurodevelopmental disorders. We regarded \geq 14 cumulative days of opioid use as “long-term opioid exposure” based on previous research indicating that long-term opioid use is infrequent in pregnancy and the median of the total days of opioid supply during pregnancy is often less than two weeks.³³

Sensitivity analyses

To our knowledge, little-to-nothing is known regarding the etiologically relevant gestational window between prenatal opioid exposure and neurodevelopmental disorders. Therefore, we conducted secondary analyses to assess the relationship between opioid exposure during specific trimesters - first

trimester (LMP to 90 days of pregnancy), second trimester (91 to 180 days of pregnancy), third trimester (181 days of pregnancy till date of birth) and the incidence of neurodevelopmental disorders.

To address the issue of exposure misclassification during specific trimester or during pregnancy, we repeated our primary analyses using an alternative exposure definition based on overlapping days of supply. Exposure misclassification can potentially occur with our primary exposure definition if, for example, a mother filled an opioid prescription close to the end of a trimester but had days of supply from previous prescription extending into the subsequent trimester. As such, infants were considered exposed during pregnancy or a specific trimester if the days' supply of opioid(s) overlapped with the pregnancy window or any trimester. Next, to overcome concerns of potential outcome misclassification, we redefined our primary outcome using two separate approaches: (a) requiring ≥ 2 hospital contacts for neurodevelopmental disorders; and (b) the presence of ≥ 2 neurodevelopmental disorders related claims on two separate days. Finally, to mitigate confounding by underlying indications for opioids, we performed two additional analyses. First, we repeated our primary analysis in a restricted cohort of children born to mothers with diagnosis of pain conditions, mental disorders or receipt of psychotropic medications. Second, we further adjusted the restricted cohort for confounding by other prespecified covariates.

RESULTS

Patients

Overall, 24,731 mothers with their 24,912 live-born infants were included in our analyses (Figure 1). There were 7.6% ($n=1,899$) infants exposed to prescription opioids during pregnancy. In four of every five exposed infants (81%, $n=1,538$), their mothers filled only one prescription of opioids during pregnancy; cumulative median dose and days of supply were 37.5 MME (2.9, 2205 MME) and 5.0 days (1, 392) respectively. Additional results on opioid utilization is presented in eTable5 in the Supplement. The median (interquartile range) and average (standard deviation (SD)) follow-up time for included

infants were 681 (252, 1397) and 890 (748.3) days respectively; the minimum and maximum follow-up time were 0 and 2558 days respectively. Prior to propensity score adjustment, compared to mothers who were unexposed, mothers who received opioids during pregnancy were older; generally had higher prevalence of tobacco use, maternal illnesses and comorbidities; and concomitant medications use (Table 1).

Outcomes

We identified 2,138 infants with neurodevelopmental disorders with 187 (9.9%) in prenatally opioid-exposed vs. 1,951 (8.5%) in unexposed infants. The crude incidence rate among exposed and unexposed infants was 42.0 and 34.7 per 1000 person-years (PY) respectively, equivalent to an unadjusted HR and 95% CI of 1.22 [1.05, 1.41] (Table 2). Following propensity-score adjustment, the risk of neurodevelopmental disorders in infants exposed prenatally to opioids was further attenuated and not statistically significant (HR: 1.16 [0.99, 1.34]). A similar finding of no significant association following adjustment was observed with our secondary outcome; developmental disorders (HR: 1.10 [0.89, 1.36]) (Table 2).

Secondary analyses

Children exposed to high cumulative opioid doses during pregnancy vs. unexposed children had increased risk of neurodevelopmental disorders (adjusted HR: 1.21 [1.01, 1.49]). Similarly, children whose mothers received at least 14 cumulative days' supply of opioids had significantly increased risks of neurodevelopmental disorders compared with unexposed children (adjusted HR: 1.66 [1.10, 2.48]) (Table 3).

Sensitivity analyses

We observed no significant association between maternal use of opioids during any specific trimester, and with alternative outcome or exposure definitions (Table 3, eTable 6). Due to sample size restrictions, we were unable to assess the relationship between maternal opioid use during ≥ 2 trimesters and

neurodevelopmental disorders in children. When we restricted our analyses to children whose mothers had pain or mental disorders conditions, or received psychotropic medications, we found no significant association after covariate adjustment (HR: 1.16 [0.94, 1.33]).

DISCUSSION

Although our findings showed an absent of significantly increased risks of neurodevelopmental disorders in children born to mothers who received prescription opioids anytime in pregnancy, or during specific trimesters of pregnancy, we observed significantly increased risks of neurodevelopmental disorders in children whose mothers received ≥ 14 days' cumulative opioid supply or higher opioid doses during pregnancy. These findings highlight the potential dangers of longer duration and higher doses of prenatal opioid exposure on children's neurodevelopment and are consistent with the known dose/exposure effects of teratogens on risks for malformations and neurodevelopmental outcomes. The majority of prescription opioid use in pregnancy is reportedly to manage acute pain,⁶ often prescribed at lower doses or for acute use (which we also observed in the current study),³³ but our findings of increased risks of neurodevelopmental disorders at high doses or longer duration of cumulative exposure have important clinical implications in women with chronic pain conditions or at risk of opioid abuse.

The exact mechanism linking prenatal opioid exposure to neurodevelopmental disorders is not fully delineated. However, opioids are known to readily cross the placenta, are present in breast milk of opioid exposed mothers, and have been reported to be capable of altering fetal brain development, particularly in women with a history of substance abuse.^{16,34} Volumetric measurements of the cerebral characteristics of children exposed to opiates during pregnancy indicated smaller intracranial and brain volumes including the cerebral cortex, amygdala, brainstem, cerebellar cortex and thinner cortex of the right lateral orbitofrontal cortex compared to unexposed infants.^{35,36} Alterations of the hippocampal cholinergic system and opiate receptor system has also been hypothesized in literature.^{34,37-39} More so,

morphine induces apoptosis of the human microglia and neurons.³⁴ Since several regions of the brain such as the limbic system, midbrain and thalamus contain the highest concentration of opioid receptors, it has been postulated that inappropriate activation of these receptors can alter the normal fetal brain development.⁴⁰

So far, evidence on this potential safety issue in human clinical studies has largely accrued from studies evaluating illicit heroin or methadone, mothers with diagnosis of substance misuse, drug dependence or OUDs, and infants with neonatal abstinence syndrome (eTable 1). Therefore, the association between maternal opioid exposure and the risk of neurodevelopmental disorders in the general population is largely unknown. Since we excluded mothers with history of OUDs and less than 0.1% of the included mothers in our study cohort had a history of substance misuse, it is difficult to index our findings to the studies previously reported in literature. To our knowledge, results at 3 and 5 years old from the Norwegian Mother and Child Cohort (MoBa) study by Skovlund et al evaluating maternal opioid use and language competencies and communications skills in children represent the only other large population-based reports evaluating this safety concern.^{41,42} The authors reported no significant association between prenatal opioid exposure and impairments in language competencies and communications skills in children at 3 or 5 years of age, but noted that their study could not address opioid use with large doses or long duration during pregnancy. While the results of our overall analysis are similar to the two reports by Skovlund et al, the current study is different in a few ways. Unlike in Skovlund's studies, we did not rely on self-reports to assess exposure status or the incidence of neurodevelopmental outcomes in children. While parental self-reporting is generally regarded as a valid tool for measuring neurocognitive disorders in children,^{43,44} there is increased propensity for recall bias with self-reported exposure. Moreover, differences between self-reported use of opioids during pregnancy compared to dispensing information available in prescription records has been reported in the MoBa cohort.⁴⁵

Additionally, neurocognitive disorders in early childhood can occur as a constellation of overlapping symptoms such that restricting to language disorders, while clinically relevant, may be too restrictive. The current study has several strengths. First, our study provides updated information on the utilization of opioids during pregnancy and extends the limited knowledge in literature on the risks associated with in-utero opioid exposure in children. Second, we utilized a relatively large population size, utilized a specific exposure definition and diagnoses for neurodevelopmental disorders as well as performed several additional analyses to mitigate confounding and to assess the robustness of our findings. Most importantly, our study provides much-needed data on relationship between cumulative dose, timing of exposure, and duration of use of opioids during pregnancy and the risk of neurodevelopmental disorders in children; information otherwise missing in the literature.

There are several limitations in the current study. Considering that administrative claims are not always reported with fidelity, measurement errors including outcome and exposure misclassification may have occurred, although more likely to be nondifferential. For example, exposure misclassification arising from the use of unprescribed or illicit opioids may have occurred. Nevertheless, the observed strength of association between our primary outcome and overall conclusions did not appreciably change with alternative exposure or more conservative outcome definitions. Second, presence of neurodevelopmental disorders is a dichotomous measure. It may therefore miss cognitive declines that do not rise to the level of a diagnosis and may have less power compared to objective continuous measures of cognitive abilities such as intelligence quotient (IQ). For example, in the NEAD study that demonstrated robust effects of valproate on IQ, an analysis for the dichotomous measure of mental retardation (i.e., <70 IQ) was not significant.⁴⁶ As such, studies involving objective measures of cognitive performance are needed to further evaluate this potential safety concern.

Despite our best efforts to address confounding by known and suspected confounders, our study results may still be impacted by residual or unmeasured confounding arising from inadequate adjustments or

incomplete information on important confounders such as maternal use of folic acid, breastfeeding patterns after delivery, lifestyle factors such as alcohol drinking during pregnancy, severity of pain, and heritability. Fourth, a variable that specifically captures the actual date of birth is absent from our data set. While we relied on validated algorithms to estimate the pregnancy period,^{47,48} and results from the replication of these methods in a database with clinically-documented date of birth (Supplementary method/results) indicated the absence of substantial bias, our estimation of the pregnancy window may still be prone to measurement error, albeit minimal. Fifth, although we included a relatively large number of mother-infant pairs, we observed low rates of neurodevelopmental disorders in children; thus, there is the concern of limited statistical power. Additionally, our findings may have been impacted by the relatively short duration of follow-up (about 2 years) as some relevant neurodevelopmental outcomes may go undetected in early infancy until later in childhood. Conversely, we may have inaccurately included false positives; that is, individuals who experienced improvements in intellectual and cognitive function later in childhood.

Finally, our study population comprises predominantly of mothers and children potentially of higher socioeconomic status or those eligible for enrollment in private health plans. Therefore, our findings may not be generalizable to uninsured or Medicaid enrolled mothers who are typically of lower socioeconomic status and thus may have a higher prevalence of risk factors predisposing children to higher risks of neurodevelopmental disorders. This specific limitation is however unrelated to the internal validity of our study.

Conclusions

Although our overall results indicate the absence of a significant association, offspring of exposed mothers prescribed opioids for a longer period or at higher cumulative dose during pregnancy had significantly increased risk of neurodevelopmental disorders. These findings emphasize the need for

careful evaluation of risks versus potential benefits in pregnant women requiring long-term opioid therapy. Further research is needed to confirm and extend the findings of our study.

Author contributions:

Author Contributions: Dr Xuerong had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Wen, Meador, Lawal.

Acquisition, analysis, or interpretation of data: Wen, Meador, Lawal, Belviso.

Drafting of the manuscript: Wen, Lawal, Meador, Belviso

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Lawal, Belviso, Shuang.

Clinical, technical, or material support: Metson, Quilliam,

Supervision: Wen, Meador.

Conflicts of interest and financial disclosures

Dr Meador has received research support from the National Institutes of Health and Sunovion Pharmaceuticals, and travel support from UCB Pharma. The Epilepsy Study Consortium pays Dr Meador's university for his research consultant time related to Eisai, GW Pharmaceuticals, NeuroPace, Novartis, Supernus, Upsher-Smith Laboratories, and UCB Pharma. XW, ODL, NB, KLM, SW, DE, and BJQ have no conflicts of interests to declare.

Funding/Support

The study is funded by grants from the National Institute of Health (NIH)/National Institute of Child Health and Human Development (NIH/NICHHD Grant number: 1R15HD097588-01; Principal Investigator: Wen X)

Role of Funder/Sponsor

The funding source had no role in the design and conduct of the study; collection, management, analysis, and the interpretation of the data preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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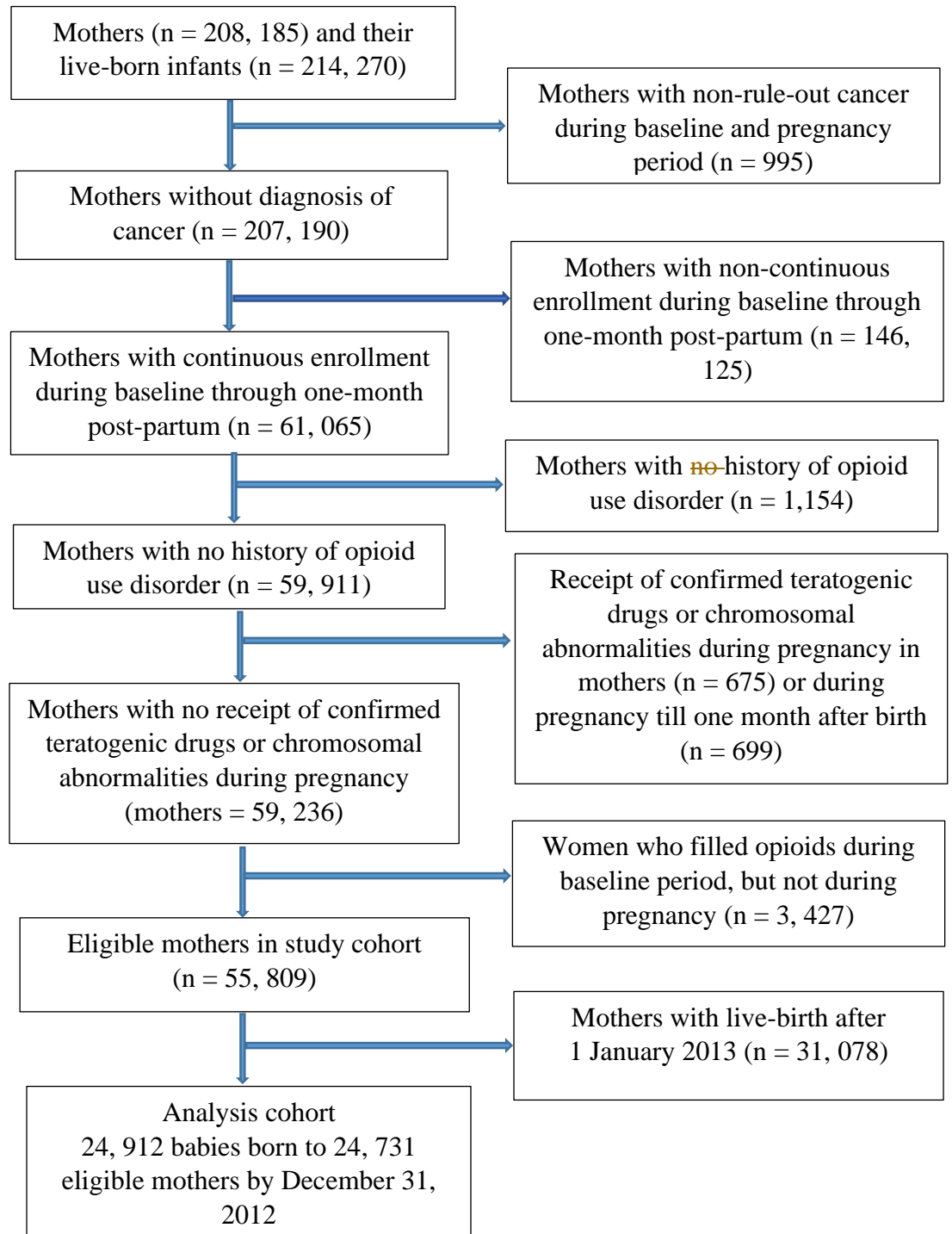
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Figure 1: Study selection



Association Between Prenatal Opioid Exposure and Neurodevelopmental Outcomes in Children

Table 1: Selected baseline characteristics of women by maternal prescription opioid use

Characteristics	Unmatched cohort			Propensity score adjusted cohort		
	Exposed (n=1899; 7.6%)	Unexposed (n=23,013; 92.4%)	Standardized difference	Exposed (n=1899; 7.6%)	Unexposed (n=22,958; 92.4%)	Standardized difference
Maternal age at delivery						
Mean age, SD	30.7 (4.3)	30.5 (4.1)	0.040	30.7 (4.3)	30.7 (4.2)	-0.040
< 18	3 (0.2)	51 (0.2)	-0.015	3 (0.2)	36 (0.2)	0.000
18 - 24	124 (6.5)	1421 (6.2)	0.015	124 (6.5)	1517 (6.6)	-0.003
25 - 34	1464 (77.1)	18292 (79.5)	-0.058	1462 (77.1)	17664 (76.9)	0.003
≥ 35	308 (16.2)	3249 (14.1)	0.059	308 (16.2)	3742 (16.3)	-0.002
Year of birth						
2010	3 (0.2)	49 (0.2)	-0.013	3 (0.2)	35 (0.2)	0.001
2011	1057 (55.7)	12171 (52.9)	0.056	1056 (55.7)	12909 (56.2)	-0.011
2012	839 (44.2)	10793 (46.9)	-0.055	838 (44.2)	10015 (43.6)	0.011
Geographic region						
Northeast	71 (3.7)	1495 (6.5)	-0.125	70 (3.7)	892 (3.9)	-0.010
Midwest	483 (25.4)	6587 (28.6)	-0.072	482 (25.4)	5751 (25)	0.008
South	782 (41.2)	8676 (37.7)	0.071	782 (41.2)	9387 (40.9)	0.007
West	553 (29.1)	6157 (26.8)	0.053	553 (29.2)	6813 (29.7)	-0.011
Unknown	10 (0.5)	98 (0.4)	0.015	10 (0.5)	117 (0.5)	0.002
Obstetric characteristics						
Tobacco use	50 (2.6)	319 (1.4)	0.089	50 (2.6)	601 (2.6)	0.002
Obesity	66 (3.5)	615 (2.7)	0.047	66 (3.5)	820 (3.6)	0.014
Multiple gestation	9 (0.5)	58 (0.3)	0.037	9 (0.5)	108 (0.5)	0.000
Substance use and abuse	2 (0.1)	10 (0)	0.023	2 (0.1)	22 (0.1)	-0.010
Obesity	66 (3.5)	615 (2.7)	0.047	66 (3.5)	820 (3.6)	0.014
Comorbid conditions						
Psychiatric conditions						
Depression	123 (6.5)	797 (3.5)	0.139	122 (6.4)	1459 (6.4)	0.028

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Anxiety	108 (5.7)	856 (3.7)	0.093	107 (5.6)	1263 (5.5)	0.024
ADHD	26 (1.4)	164 (0.7)	0.065	26 (1.4)	315 (1.4)	-0.002
Bipolar disorder	10 (0.5)	39 (0.2)	0.061	9 (0.5)	112 (0.5)	0.018
Epilepsy	4 (0.2)	33 (0.1)	0.016	4 (0.2)	46 (0.2)	0.017
ADHD	26 (1.4)	164 (0.7)	0.065	26 (1.4)	315 (1.4)	-0.002
Pain conditions						
Fibromyalgia	52 (2.7)	417 (1.8)	0.062	52 (2.7)	628 (2.7)	0.004
Migraine	196 (10.3)	934 (4.1)	0.244	195 (10.3)	2330 (10.2)	0.005
Back pain	510 (26.9)	3707 (16.1)	0.264	510 (26.9)	6407 (27.9)	-0.019
Other maternal illnesses						
Diabetics	29 (1.5)	302 (1.3)	0.018	29 (1.5)	344 (1.5)	-0.011
Hypertension	44 (2.3)	321 (1.4)	0.068	44 (2.3)	522 (2.3)	0.010
Renal disease	12 (0.6)	57 (0.2)	0.058	12 (0.6)	144 (0.6)	0.001
Concomitant medication use						
Psychotropic medications						
Benzodiazepines	121 (6.4)	504 (2.2)	0.208	120 (6.3)	1392 (6.1)	0.018
Antidepressants	240 (12.6)	1323 (5.7)	0.240	239 (12.6)	2870 (12.5)	0.030
Psychostimulants	44 (2.3)	248 (1.1)	0.096	44 (2.3)	522 (2.3)	0.005
Antipsychotics	5 (0.3)	36 (0.2)	0.023	4 (0.2)	57 (0.2)	-0.003
Other medications						
Antidiabetics	57 (3)	430 (1.9)	0.074	57 (3)	693 (3)	-0.005
Antihypertensives	79 (4.2)	467 (2)	0.123	79 (4.2)	898 (3.9)	0.022
Antiepileptics	38 (2)	141 (0.6)	0.122	37 (2)	393 (1.7)	0.028
Maternal comorbidity makers						
Maternal comorbidity index, mean (SD)	0.4 (0.8)	0.3 (0.7)	0.068	0.4 (0.8)	0.4 (0.8)	0.015
Number of hospitalizations	1.2 (2.7)	1.1 (1.9)	0.039	1.2 (2.7)	1.2 (2.7)	0.023
Length of hospitalization, mean (SD)	0.4 (0.5)	0.5 (0.5)	-0.043	0.4 (0.5)	0.4 (0.5)	0.031
Number of outpatient visits, mean (SD)	33.4 (25)	30.9 (24.2)	0.100	33.4 (25.0)	32.7 (26.8)	0.027

Abbreviations. ADHD, attention-deficit hyperactivity disorder; PS, propensity scores. Unless otherwise stated, number (%) are presented.

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Table 2: Hazards ratio of the risk of neurodevelopmental disorders in children by maternal exposure to opioids

Outcome	Total number	Cases, n (%)	Incidence rate per 1000 PY	Crude HR (95% CI)	Adjusted HR (95% CI) ^a
Neurodevelopmental disorders					
Unexposed	23013	1951 (8.5)	34.7	1	1
Exposed	1899	187 (9.9)	42.0	1.22 (1.05, 1.41)	1.16 (0.99, 1.34)
Developmental disorders					
Unexposed	23013	1292	22.9	1	1
Exposed	1899	120	26.9	1.17 (0.97, 1.42)	1.10 (0.89, 1.36)

Abbreviations. HR, Hazards ratio; PY, person-years; n, number. ^a Adjusted HRs and 95% CI were obtained using propensity score by fine stratification

Table 3: Sensitivity analyses of the risk of neurodevelopmental disorders in children by maternal opioid use

Additional analyses	Total number	Case	IR per 1000 PY	Unadjusted HR	Adjusted HR ^a
Timing of exposure during pregnancy					
Unexposed	23013	1951	34.7	1	1
First trimester alone	653	66	42.7	1.23 (0.98, 1.58)	1.10 (0.86, 1.41)
Second trimester alone	395	36	39.8	1.15 (0.83, 1.62)	1.11 (0.80, 1.54)
Third trimester alone	672	66	41.3	1.19 (0.94, 1.54)	1.20 (0.94, 1.54)
Cumulative duration of use during pregnancy					
Unexposed	23013	1951	34.7	1	1
Less than 14 days	1717	163	40.2	1.20 (1.03, 1.40)	1.12 (0.95, 1.31)
At least 14 days	182	24	59.0	1.72 (1.16, 2.53)	1.66 (1.10, 2.48)
Cumulative dose ^b					
Unexposed	23013	1951	34.7	1	1
Low dose (<37.5 MME)	986	88	38.8	1.14 (0.92, 1.40)	1.10 (0.87, 1.36)
High dose (≥37.5 MME)	913	99	45.3	1.36 (1.12, 1.65)	1.21 (1.01, 1.49)
Alternative outcome definitions					
≥ 2 mental disorder claims					
Unexposed	23013	1462	26.0	1	1
Exposed	1899	133	29.8	1.15 (0.97, 1.38)	1.10 (0.91, 1.35)
≥2 mental disorders claims filled on ≥2 separate days					
Unexposed	23013	1023	18.2	1	1
Exposed	1899	89	20.0	1.10 (0.89, 1.37)	1.06 (0.84, 1.34)
Analysis in restricted cohort with diagnosis of pain or mental disorders, or receipt of psychostimulants					
Unexposed	12337	823	27.8	1	1
Exposed	1246	95	32.9	1.20 (1.01, 1.44)	1.16 (0.94, 1.44)

Abbreviations. HR: hazards ratio; IR: incidence rate; PY: person-years; MME: morphine milligram equivalent. ^a Adjusted HRs and 95% CI were obtained using propensity score by fine stratification. ^b Fetal cumulative opioid exposure was categorized by median split of the total opioid doses during pregnancy. The low and high categories correspond to 2.25 – 37.4 MME and 37.5 – 2250 MME respectively.