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Paternal preconception exposure to non-steroid anti-inflammatory drugs or opioids and adverse birth outcomes

A nationwide registry-based cohort study

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Title: Paternal preconception exposure to non-steroid anti-inflammatory drugs or opioids and adverse birth outcomes: A Nationwide registry-based cohort study

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ABSTRACT

Background and aim

Paternal use of analgesics during the time of conception and adverse birth outcomes is poorly studied. We investigated the association between paternal exposure to Non-Steroid Anti-inflammatory Drugs (NSAIDs) and opioids within 3 months before the date of conception and the risk of adverse birth outcomes (preterm birth, small for gestational age (SGA), low Apgar score, and major congenital malformations (MCMs).

Methods

We used nationwide data from the Danish health registers. We included information on all singleton live birth, and their father and mother from 1997 to 2018. We created two exposed cohorts, children with preconception paternal exposure to i) NSAIDs and ii) opioids. The unexposed cohort was children without preconception paternal exposure to NSAID or opioids, and we performed a sub-analysis against paternal use of acetaminophen (paracetamol). We used logistic regression models to estimate the odds ratios (OR) of adverse birth outcomes including 95% confidence intervals (95% CI).

Results

We identified 1,260,934 children, 45,667 children with paternal exposure to NSAIDs, 10,086 children with paternal exposure to opioids, and 1,205,181 unexposed children. The adjusted OR for preterm birth was 1.08 (95% CI, 1.03-1.13) after paternal exposure to NSAIDs and 1.21 (95% CI, 1.08-1.35) after paternal exposure to opioids. The adjusted OR for SGA was 1.09 (95% CI, 1.03-1.17) after paternal exposure to NSAIDs, and 1.03 (95% CI, 0.88-1.21) after paternal exposure to opioids. We found null-associations for a low Apgar score and MCMs. Estimates were attenuated when compared against paternal paracetamol exposure.

Conclusions

Overall, we found null-associations across the comparisons made. Weak associations were found for paternal exposure to NSAIDs or opioids and preterm birth and SGA, but not with low Apgar score or MCM. All associations were attenuated when compared against an active comparator of paternal paracetamol exposure. The effect sizes were small and less likely to be of clinical relevance.

Keywords: Paternal, preconception, NSAIDs, opioids, adverse birth outcomes

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INTRODUCTION

The health of expecting parents, and their use of medications, is of importance for the developing fetus.[1] Aspects of the maternal contribution have been a focus of reproductive research for decades while paternal exposure has been poorly studied.[2-4] Evidence of paternal exposure to medication, before conception and around the time of spermatogenesis, is starting to accumulate, and an increased risk of adverse birth outcomes has been reported.[2,5-7] Several metabolites from medication can be found in semen and may potentially have direct genetic or epigenetic effects on the sperm cell. This hypothesis is supported by some preclinical data.[8,9]

Scandinavian studies have recently reported that up to 38% of expecting fathers in the preconception period use analgesics and the use is increasing.[10,11] In Denmark, the majority of Non-Steroid Anti-Inflammatory Drugs (NSAIDs) and all opioids are administered only by prescription, except for low-dose (200mg) ibuprofen with <20 tables that are sold over-the-counter. NSAIDs are widely used in pain management as an analgesic and anti-inflammatory treatment in musculoskeletal and autoimmune diseases.[6,10,12] NSAIDs inhibit the cyclooxygenase (COX-1 and 2) and influence the prostaglandin synthesis which potentially has implications on reproduction outcomes. [8,13,14] Collectively, exposure to different doses of NSAIDs has shown a negative effect on semen quality.[8,14,15] Two Norwegian cohort studies have examined the risk of adverse birth outcomes after paternal drug exposure, and in pooled analyses with up to 20 different drugs including NSAIDs, they did not find an increased risk for spontaneous abortions, preterm births, perinatal mortality, small for gestational age (SGA), or congenital malformations.[6,16] Paternal exposure to NSAIDs before the time of conception was not examined separately for the risk of adverse birth outcomes.[6,16] Like NSAIDs, opioids are commonly prescribed for moderate to severe pain conditions for short-term pain alleviation. Cannabis and codeine may result in epigenetic changes through changes in the sperm DNA methylation or may induce oxidative stress leading to sperm DNA fragmentation.[9,17] Either may potentially have implications on reproductive outcomes.[9,17] In Denmark, the paternal prescriptions of opioids before the time of conception increased from 1% to 2.3% from 1997 to 2017.[11] Paternal exposure to NSAIDs or opioids is relevant up to three months before the time of conception corresponding to the spermatogenesis.[7,18]

We studied the association between paternal-filled prescriptions of either NSAIDs or opioids within three months before the time of conception and adverse birth outcomes. The adverse birth outcomes of interest were preterm birth, SGA, low Apgar score, and major congenital malformations (MCMs).

MATERIAL AND METHODS

Data sources

This was a nationwide cohort study based on Danish health registers. We used data from the I) Danish Medical Birth Register, which has obtained information on all births in Denmark since 1973 and includes data on the neonate, father, mother, pregnancy-related data, and information on birth outcomes.[19,20] II) The Danish National Patient Register includes information on hospitalization, and

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outpatient visits for the entire Danish population since 1977, including information on the place, dates of admission and discharge, procedures performed and diagnoses registered based on the International Classification of Diseases (ICD-8 before 1994, and ICD-10 from 1994 and onwards).[21] III) The Danish National Prescription Register includes data on all filled prescriptions in Denmark since 1 January 1995, and data includes key information from all Danish pharmacies. The medication is classified according to the Anatomical Therapeutical Chemical (ATC) classification system.[22] IV) The Central Personal Registration system provides information on death and migration based on the assignment of a unique civil registration number of each citizen at birth or immigration and is an exceptional system for valid record linkage at an individual level across registries.[23]

Study population

The study population comprised all live-born singleton children, born in Denmark from 1 January 1997 until 31 December 2018, identified in the Danish Medical Birth Register, and the registered father and mother of the child. We included data on both paternal and maternal use of medication before conception. We excluded children with paternal exposure to methadone (ATC: N07BC02), fentanyl for anesthetic use (ATC: N01AH01), or codeine (ATC: N02AJ06, N02AJ07) within 1 year before conception. We chose to exclude these exposures used for treating drug addiction or in relation to surgery, and also codeine as only a small amount is converted to morphine. We excluded children with paternal exposure to methotrexate within 3 months before conception, because of the adverse effects on spermatogenesis.[24-26] We excluded children whose fathers had any surgery within 3 months before conception as this group of patients is heterogenic with many different underlying diseases or conditions. Finally, we excluded children with maternal exposure to any medication with a suspected teratogenic effect (30 days before conception or during pregnancy: retinoids, angiotensin-converting enzyme inhibitors, vitamin K antagonists, valproic acid, lithium, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, or methotrexate).[27]

The exposed and unexposed cohorts

We used one filled prescription within 3 months before the date of conception for paternal use of NSAIDs or opioids to create two cohorts of exposed children, those with paternal exposure to NSAIDs and those with paternal exposure to opioids. The exposure to NSAIDs or opioids was based on prescriptions for NSAIDs (ATC: M01A (excluding M01AX05 (Glucosamine))) and opioids (ATC: N02AA01, N02AA05, N02AA55, N02AB03, N02AX02, N02AX06) from the Danish National Prescription Register. The unexposed cohort consisted of all children without paternal exposure to NSAIDs or opioids. The date of conception was calculated using the expected gestational age registered in the Danish Medical Birth Register. The expected gestational age was defined by clinical examination or estimated by fetal ultrasound in the Danish Medical Birth Register. We created an additional cohort for a sub-analysis comprising fathers who filled a prescription for acetaminophen (paracetamol) within three months prior to conception.

Outcome ascertainment

The adverse birth outcomes of interest were preterm birth, SGA, low Apgar score, and MCMs. Preterm birth was defined as birth before 37 completed weeks of pregnancy. SGA was defined by a

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birth weight below the mean -2 standard deviation according to gestational age and sex.[28] The 5-minute Apgar score was used for the evaluation of five clinical signs with a summarized score between 0-10, and it was dichotomized as normal (≥7) and low (<7). A score below 7 is recognized as a marker for the severity of neurologic impairments.[29,30] Preterm birth, SGA, and the Apgar score were identified in the Danish Medical Birth Register. MCMs were classified according to The European Surveillance of Congenital Anomalies (EUROCAT) guidelines using ICD-10 codes from the Danish National Patient Register detected within one year after birth.[31]

Confounders

From the Danish Medical Birth Register, we retrieved information on paternal age and maternal age at the time of childbirth, sex of the child, parity (categorized as one or more than one previous childbirth), maternal smoking during pregnancy (no/yes), calendar year of birth in four categories (1997-2002, 2003-2008, 2009-2014 and 2015-2019). From the National Patient Register, we used diagnoses related to paternal and maternal comorbidity retrieving information on diseases within 6 months before conception in categories (ICD-10 including all subgroups); mental disorders (F), central nervous system disorders (G), circulatory disorders (I), lung disease (J), digestive disorders (K), musculoskeletal disorders (M), cancer (C), and dermatologic disorder (L). We retrieved information on paternal exposure to paracetamol within 3 months before the date of conception from the Danish National Prescription Register.

Statistical analysis

A contingency table was conducted for the main study variables according to the two exposed cohorts and the unexposed cohort. When examining the risk of preterm birth, SGA, low Apgar score, and MCMs, we used logistic regression models. We computed the crude and the adjusted odds ratios (OR) with corresponding 95% confidence intervals (95% CI) following paternal exposure to NSAIDs or opioids within 3 months before conception, relative to the unexposed cohort. Adjustments were made for paternal age (in categories), paternal disease within 6 months before conception, paternal exposure to NSAIDs within 3 months before conception (only in the opioids analysis), paternal exposure to opioids within 3 months before conception (only in the NSAIDs analysis), paternal exposure to paracetamol within 3 months before conception, maternal age (in categories), maternal disease within 6 months before conception, parity, maternal smoking in pregnancy, sex of the child, and calendar year of childbirth (in categories). All calculations were made using STATA Release 17.0.

Sensitivity and sub-analyses

In a sensitivity analysis, we required two filled prescriptions for paternal exposure to NSAIDs or opioids within 3 months before the date of conception.

In a sub-analysis examining the outcomes of preterm birth, SGA, and low Apgar score, we excluded children born by women with pregnancy complications (pregnancy increased blood pressure (ICD10: O10, O13), preeclampsia (ICD10: O11, O14), eclampsia (ICD10: O15), or gestational diabetes (ICD10: O224, O249)).[32] In another sub-analysis, we compared adverse birth outcomes in children with paternal exposure to NSAIDs or opioids to children born to fathers with preconception exposure to paracetamol 3 months before the date of conception. We used an active comparative group to mitigate potential confounding by indication, as the prescription of paracetamol indicates a level of pain that is likely less severe than among those prescribed an opioid or NSAID. In this analysis, we

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excluded fathers in all cohorts, if they were exposed to a combination of paracetamol with NSAIDs or paracetamol with opioids.

Approvals and ethics

The study was approved by the Danish Data Protection Agency (j.nr. 20/4674). According to Danish law and legislation, no patient approvals are required for observational register-based studies.

Patient involvement

We have presented the initial idea for patients and relatives represented in the local research council for the Center for Clinical Epidemiology and the Research Unit for Clinical Epidemiology at Odense University Hospital and the University of Southern Denmark, respectively. They have contributed to important discussions of the study conceptualization, identification of outcomes, and during the analytic process with a discussion on the preliminary results.

RESULTS

We identified 1,260,934 children born from 1997-2018 in the Danish registers. Within three months prior to conception, there were a total of 45,667 children with paternal exposure to NSAIDs, 10,086 children with paternal exposure to opioids, and 1,205,181 children without paternal exposure to NSAIDs or opioids, Supplementary Figure 1. The paternal median age in the three cohorts of NSAIDs, opioids, and unexposed was 32 years (percentile 25-75: 28-36), 33 years (percentile 25-75: 29-37), and 31 years (percentile 25-75: 28-35), respectively. Musculoskeletal disorders were present in 10.2% of the fathers in the NSAIDs cohort and in 20.4% of the fathers in the opioid cohort 6 months before the time of conception. In the unexposed children, paternal musculoskeletal disorders were present in 2.2%, and in 94.2% of the children, the father had no hospital-diagnosed diseases. See Table 1 for more characteristics of the exposed and unexposed cohorts of children and their parents. In Supplementary Table 1, the sub-distribution of NSAIDs and opioids according to the number of prescriptions is available.

In our exposed cohorts, we found that around 5.5-6.0% were born preterm. In the unexposed cohort, 5% were born preterm. The percentage of SGA children was about 3.0% in the exposed cohorts, and 2.7% in the unexposed. The percentage with low Apgar score was almost even or smaller than 1% in the exposed cohorts and under 1% in the unexposed. MCMs were present in around 4.0% of the exposed cohorts, and 3.6% in the unexposed. When comparing the exposed cohorts to the unexposed cohorts, we observed a statistically significant OR for preterm birth of 1.08 (95% CI, 1.03-1.13) for children with paternal exposure to NSAIDs and an OR for preterm birth of 1.21 (95% CI, 1.08-1.35) for children with paternal exposure to opioids (Table 2). We observed a statistically significant OR for SGA 1.09 (95% CI, 1.03-1.17) for children with paternal exposure to NSAIDs compared to the unexposed. We did not observe increased ORs for low Apgar scores and MCMs for children with paternal exposure to NSAIDs or opioids (Table 2).

In the sensitivity analysis, we required two filled prescriptions for preconception paternal exposure to NSAIDs or opioids, we did not find any changes in our conclusions (data not shown). In the sub-analysis on preterm birth, SGA, and low Apgar score where children born by mothers, who

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experienced pregnancy complications were excluded, the adjusted OR for preterm birth decreased to 1.06 (95% CI, 1.01-1.12) and 1.15 (95% CI, 1.02-1.13) for children with paternal preconception exposure for NSAIDs or opioids exposure, respectively. This analysis did not change any of the other risk estimates (Table 3). In the sub-analysis using paracetamol as the reference, we did not observe any statistically significant estimates for any outcomes, e.g. the risk for preterm birth was 0.89 (95% CI, 0.75-1.07) and 1.10 (95% CI, 0.89-1.36) for children with paternal preconception exposure for NSAIDs or opioids exposure, respectively (Table 4).

DISCUSSION

This observational cohort study is the first controlled study to examine preconception paternal exposure to NSAIDs and exposure to opioids on adverse birth outcomes. Our results were reassuring regarding the risk of preterm birth, SGA, low Apgar score, and MCMs after preconception paternal exposure to NSAIDs, and exposure to opioids. In the exposed children were approximately 5.5% born preterm, 3% had SGA, <1% had low Apgar score, and 4% were born with MCMs, and these percentages were almost the same in the unexposed children. We did not observe any strong evidence for increased risk according to our risk estimates for preterm birth and SGA, and we did not find any association between the exposures and low Apgar scores or MCMs. In three sensitivity/sub-analyses, we 1) used a more restrictive definition with two prescriptions for paternal exposure to NSAIDs or opioids in the preconception period, 2) excluded children whose mothers had pregnancy complications, and 3) used paternal exposure to paracetamol as the comparator. These analyses confirmed our initial results and the risk for preterm birth after preconception paternal exposure to NSAIDs was reduced in the restricted population without pregnancy complications, and all risks were attenuated when compared against the comparator group exposed to paracetamol. Paternal preconception exposure to paracetamol and child outcomes is insufficiently studied. Clinical data does not suggest changes to sperm count or motility.[33]

Preterm birth may be facilitated by many different mechanisms, most of which are maternal.[34] It is recognized that the precise mechanism is not determined in many cases, and information on risk factors from a paternal perspective is sparse. The importance of some preconception paternal exposures on adverse birth outcomes have been reported.[2,5-7] Socioeconomic factors are important[35] and it could be hypothesized the paternal use of prescribed analgesics to some extent are proxies for suboptimal familial circumstances affecting the course of pregnancy. Nonetheless, various paternal preconception factors may affect the offspring, and several potential mechanisms may coexist, e.g. heritable epigenetic modifications encoded in the sperm, chemical exposures may induce changes to the DNA methyltransferase or histone deacetylase activity may increase the risk of diseases in the offspring.[36] We found a weak association between preterm birth and paternal exposure to NSAIDs and opioids. The risk was attenuated when we omitted children whose mothers had experienced pregnancy complications. Studies on multiple preconception paternal exposures have used a different analytic approach with the pooling of several drugs.[6,16] Engeland et al.[6] report no increased odds of adverse pregnancy- and birth outcomes (spontaneous abortion, preterm birth, perinatal mortality, SGA, and MCMs in a pooled analyses on exposure to one or more of 20 selected drugs including NSAIDs and opioids. These previous results from Engeland et al.[6] are supported by

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our results on opioid exposure and the risk of adverse birth outcomes. Viktil et al.[16] found that paternal exposure to NSAIDs was relatively rare, and they did not observe any trends with adverse birth outcomes.

Data on the risk of adverse birth outcomes (e.g. MCMs) after paternal exposure to medications prior to conception are sparse and make direct comparison difficult. In our study, there was a null-association between paternal exposure to NSAIDs or opioids, and MCMs. Similar reassuring results for the risk of MCMs have been shown by our group for medications such as 5-aminosalicylic acid, thiopurines, corticosteroids, and anti-tumor necrosis factor-α in a cohort of children where the father was diagnosed with inflammatory bowel disease.[37,38] Reassuringly, a null-association between preconception paternal exposure to methotrexate, known to be an in-utero exposure teratogen, and MCMs has been shown.[26] In a Swedish birth cohort, paternal exposure to antiepileptic drugs was not associated with MCMs.[39] Few paternal exposures to medication, e.i. metformin and sulfonylureas have been associated with a minor increased risk of MCMs, even though the biological rationale is unclear.[40] Our result for MCMs and paternal exposure to NSAIDs or opioids is indeed in line with the previous reassuring results for some types of medication. When examining MCMs, our study used the EUROCAT classification with ICD-10 coding for live-born children and hereby we did not account for MCMs diagnosed in utero. The rate of malformations among second-trimester induced abortions was 14% in a Danish study and 4% of pregnancies were terminated in the second trimester.[41] The overall impact of this potential misclassification is likely low.

This study has several strengths. The study benefits from a nationwide design allowing us to create two large exposed cohorts and one unexposed cohort ensuring the power to study rare adverse birth outcomes from 1997-2018. The Danish health registers are considered to hold valid information with a degree of completeness on procedures, diagnoses, and filled prescriptions for medication and the ability to link data on the father, mother, and child.[21-23] By using filled prescriptions on NSAIDs and opioids to define paternal exposure we eliminate the possibility of recall bias. One could argue that misclassification could still be an issue, however, if there are any misclassifications in the register data it would be non-differential making our risk estimates towards the null hypothesis. Potential non-differential use of NSAIDs from over-the-counter sales cannot be accounted for. Since only NSAIDs (e.g. ibuprofen) with low doses and in small volumes are available over-the-counter this may be a minor issue although this non-differential misclassification will bias towards the null. The adverse birth outcomes that we studied were independently collected from the Danish Medical Birth Register and the National Patient Register, and the paternal drug exposure was collected from the Danish National Prescription Register. In our analyses, we adjust for a priori selected confounders related to both parents and the child. For instance, in an attempt to adjust for potential paternal and maternal underlying diseases in a 6-month preconception period, we used a wide palette of ICD-10 codes. Limitations are inherent to the observational nature of the study; the possibility of bias, residual confounding, and the influence of unknown confounders cannot be ruled out. For example, we were not able to include information on dosing or indication for preconception paternal drug exposure as this information is not available from the register. Another limitation was the available data from the registers, e.g., we had some missing information on mothers smoking status in the first years of our study period, and children with missing information were excluded in the adjusted regression models limiting the number of children included.

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CONCLUSIONS

In this unselected nationwide registry-based study, we found no clinically important associations between paternal exposure to NSAIDs or opioids and adverse pregnancy outcome of preterm birth, SGA, low APGAR score, or the risk of MCMs. Our primary analysis identified weak associations between both exposures and preterm birth and between NSAID exposure and SGA, all of which were attenuated when compared against an active comparator.

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None to declare.

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Author contribution

KL, BMN, and LRJ were involved in the conception and design of the study. KL wrote the original draft, assisted with data analyses, and reviewed and edited the draft for intellectual content. BMN and LRJ assisted with the design of the study, assisted with data analyses, and reviewed and edited for intellectual content. OSG collected and did the formal data analyses, and reviewed and edited the draft for intellectual content. SMA assisted with the data collection and data analysis. PD assisted with the design of the study, assistance with data analyses, and reviewed and edited for intellectual content. MDL assisted with the design of the study and reviewed and edited for intellectual content. The final manuscript was approved by all authors.

Conflict of interest

The authors declare no conflict of interest.

Data accessibility

We used data from the Danish health registers, and our study has the appropriate approvals according to Danish law. However, the data used for this study must not be shared open access with other parties according to legislation. Access to the data from the Danish health registers is by application to the Danish Data Authority (forskerservice@sundhedsdata.dk). Approval for access to the data is needed from the Danish Data Protection Agency. We do not have any special privileges to access the data used for this study.

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Legends and Tables

Table 1: Characteristics of children with paternal exposure to NSAIDs or opioids and children without paternal exposure to NSAIDs or opioids within 3 months before the date of conception from 1997-2018.

	Children with paternal exposure to NSAIDs within 3 months before the date of conception n = 45,667	Children with paternal exposure to opioids within 3 months before the date of conception n = 10,086	Children without paternal exposure to NSAIDs or opioids within 3 months before the date of conception n = 1,205,181
	n (%)	n (%)	n (%)
Paternal age at conception, years			
Median (p25-p75)	32 (28-36)	33 (29-37)	31 (28-35)
Paternal age at conception, in categories			
<30	14,980 (32.8)	2,940 (29.1)	438,652 (36.4)
30-35	17,737 (38.8)	3,660 (36.3)	488,820 (40.6)
>35	12,943 (28.3)	3,485 (34.6)	277,658 (23.0)
Paternal disease within 6 months before conception			
None	38,510 (84.3)	7,092 (70.3)	1,134,836 (94.2)
Mental disorders	190 (0.4)	113 (1.1)	2,239 (0.2)
Central nervous system disorders	753 (1.6)	330 (3.3)	8,539 (0.7)
Circulatory disorders	473 (1.0)	199 (2.0)	7,064 (0.6)
Lung diseases	558 (1.2)	200 (2.0)	8,754 (0.7)
Digestive disorders	812 (1.8)	373 (3.7)	14,567 (1.2)
Musculoskeletal disorder	4,648 (10.2)	2,058 (20.4)	26,108 (2.2)
Cancer	103 (0.2)	42 (0.4)	2,364 (0.2)
Paternal exposure to opioids within 3 months before the date of conception			

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No	41,667 (91.2)	-	-
Yes	4,000 (8.8)	-	-
Paternal exposure to NSAIDs within 3 months before the date of conception			
No	-	6,086 (60.3)	-
Yes	-	4,000 (39.7)	-
Paternal exposure to paracetamol within 3 months before the date of conception			
No	41,054 (89.9)	8,059 (79.9)	1,201,777 (99.7)
Yes	4,613 (10.1)	2,027 (20.1)	3,404 (0.3)
Maternal age at conception, years			
Median (p25-p75)	30 (26-33)	30 (26-34)	30 (27-33)
Maternal age at conception, in categories			
<30	21,561 (47.2)	4,687 (46.5)	562,931 (46.7)
30-35	17,503 (38.3)	3,764 (37.3)	482,960 (40.1)
>35	6,587 (14.4)	1,630 (16.2)	159,117 (13.2)
Maternal disease within 6 months before conception			
None	41,708 (91.3)	8,969 (88.9)	1,113,571 (92.4)
Mental disorders	176 (0.4)	62 (0.6)	3,672 (0.3)
Central nervous system disorders	471 (1.0)	159 (1.6)	10,856 (0.9)
Circulatory disorders	276 (0.6)	76 (0.8)	7,115 (0.6)
Lung diseases	462 (1.0)	120 (1.2)	11,851 (1.0)
Digestive disorders	1,032 (2.3)	305 (3.0)	23,913 (2.0)
Musculoskeletal disorder	1,445 (3.2)	407 (4.0)	31,138 (2.6)
Cancer	72 (0.2)	16 (0.2)	1,816 (0.2)
Maternal smoking			
No	33,931 (74.3)	7,256 (71.9)	944,470 (78.4)
Yes	8,369 (18.3)	2,370 (23.5)	165,727 (13.8)
Missing	3,367 (7.4)	460 (4.6)	94,984 (7.9)
Parity			
First	17,911 (39.2)	3,665 (36.3)	535,349 (44.4)
Second or more	27,279 (59.7)	6,330 (62.8)	657,211 (54.5)
Missing	477 (1.0)	91 (0.9)	12,621 (1.0)

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Sex of the child			
Girl	21,992 (48.2)	4,891 (48.5)	586,544 (48.7)
Boy	23,675 (51.8)	5,195 (51.5)	618,637 (51.3)
Calendar year of birth			
1997-2002	12,690 (27.8)	1,425 (14.1)	344,671 (28.6)
2003-2008	14,251 (31.2)	2,544 (25.2)	338,182 (28.1)
2009-2014	11,193 (24.5)	3,495 (34.7)	310,201 (25.7)
2015-2018	7,533 (16.5)	2,622 (26.0)	212,127 (17.6)

Table 2: Comparison of adverse birth outcomes in children with paternal exposure to NSAIDs or opioids to children without paternal exposure within 3 months before the date of conception from 1997-2018.

	Events/Total (%)	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Preterm birth			
Unexposed	59,679/1,205,181 (5.0)	1	1
NSAIDs exposed	2,483/45,667 (5.4)	1.10 (1.06-1.15)	1.08 (1.03-1.13)
Opioids exposed	600/10,086 (5.9)	1.21 (1.12-1.32)	1.21 (1.08-1.35)
Small for gestational age			
Unexposed	31,838/1,197,673 (2.7)	1	1
NSAIDs exposed	1,361/45,398 (3.0)	1.13 (1.07-1.20)	1.09 (1.03-1.17)
Opioids exposed	322/10,027 (3.2)	1.21 (1.09-1.36)	1.03 (0.88-1.21)
Low APGAR Score			
Unexposed	8,859/1,196,325 (0.7)	1	1
NSAIDs exposed	365/45,343 (0.8)	1.09 (0.98-1.21)	1.05 (0.93-1.18)
Opioids exposed	90/9,998 (0.9)	1.22 (0.99-1.50)	1.00 (0.74-1.35)
Major Congenital Malformations			
Unexposed	43,244/1,196,538 (3.6)	1	1
NSAIDs exposed	1,680/45,412 (3.7)	1.02 (0.97-1.07)	1.02 (0.97-1.08)
Opioids exposed	412/10,034 (4.1)	1.14 (1.03-1.25)	1.07 (0.93-1.22)

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[a]Adjusted by: Paternal age (in categories), paternal disease within 6 months before conception, paternal exposure to NSAIDs within 3 months before conception (only in the opioid analysis), paternal exposure to opioids within 3 months before conception (only in the NSAIDs analysis), paternal exposure to acetaminophen (paracetamol) within 3 months before conception, maternal age (in categories), maternal disease within 6 months before conception, parity, maternal smoking in pregnancy, sex of the child, and calendar year of childbirth (categories).

Table 3: Comparison of adverse birth outcomes in children with paternal exposure to NSAIDs or opioids to children without paternal exposure within 3 months before the date of conception from 1997-2018 **excluding children with maternal pregnancy complications**[a].

	Events/Total (%)	Crude OR (95% CI)	Adjusted[b] OR (95% CI)
Preterm birth			
Unexposed	49,889/1,126,623 (4.4)	1	1
NSAIDs exposed	2,040/42,398 (4.8)	1.09 (1.04-1.14)	1.06 (1.01-1.12)
Opioids exposed	475/9,228 (5.1)	1.17 (1.07-1.29)	1.15 (1.02-1.31)
Small for gestational age			
Unexposed	26,376/1,119,541 (2.4)	1	1
NSAIDs exposed	1,112/42,144 (2.6)	1.12 (1.06-1.19)	1.07 (0.99-1.14)
Opioids exposed	250/9,173 (2.7)	1.16 (1.02-1.32)	0.94 (0.78-1.12)
Low APGAR Score			
Unexposed	7,833/1,118,472 (0.7)	1	1
NSAIDs exposed	315/42,107 (0.7)	1.07 (0.95-1.20)	1.04 (0.92-1.19)
Opioids exposed	77/9,149 (0.8)	1.20 (0.96-1.51)	1.01 (0.73-1.41)

[a]Maternal pregnancy complications: pregnancy increased blood pressure, preeclampsia, eclampsia, or gestational diabetes.

[b]Adjusted by: Paternal age (in categories), paternal disease within 6 months before conception, any paternal surgery within 6 months before conception, paternal exposure to NSAIDs within 3 months before conception (only in the opioid analysis), paternal exposure to opioids within 3 months before conception (only in the NSAIDs analysis), paternal exposure to acetaminophen (paracetamol) within 3 months before conception, maternal age (in categories), maternal disease within 6 months before conception, parity,

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maternal smoking in pregnancy, sex of the child, and calendar year of childbirth (categories).

Table 4: Comparison of adverse birth outcomes in children with paternal exposure to NSAIDs or opioids to children with **paternal exposure to paracetamol** within 3 months before the date of conception from 1997-2018

	Events/Total (%)	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Preterm birth			
Paracetamol reference	189/3404 (5.6)	1	1
NSAIDs exposed	2221/41054 (5.4)	0.97 (0.84-1.13)	0.89 (0.75-1.07)
Opioids exposed	474/8059 (5.9)	1.06 (0.89-1.26)	1.10 (0.89-1.36)
Small for gestational age			
Paracetamol reference	96/3381 (2.8)	1	1
NSAIDs exposed	1228/40811 (3.0)	1.06 (0.86-1.31)	0.90 (0.70-1.15)
Opioids exposed	251/8012 (3.1)	1.11 (0.87-1.41)	0.73 (0.54-0.98)
Low APGAR Score			
Paracetamol reference	33/3372 (1.0)	1	1
NSAIDs exposed	319/40775 (0.8)	0.80 (0.56-1.14)	0.77 (0.51-1.18)
Opioids exposed	66/7988 (0.8)	0.84 (0.55-1.28)	0.69 (0.39-1.20)
Major Congenital Malformations			
Paracetamol reference	154/3382 (4.6)	1	1
NSAIDs exposed	1470/40829 (3.6)	0.78 (0.66-0.93)	0.94 (0.78-1.15)
Opioids exposed	329/8015 (4.1)	0.90 (0.74-1.09)	0.99 (0.77-1.26)

[a]Adjusted by: Paternal age (in categories), paternal disease within 6 months before conception, maternal age (in categories), maternal disease within 6 months before conception, parity, maternal smoking in pregnancy, sex of the child, and calendar year of childbirth (categories).

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