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Early View

ORIGINAL ARTICLE

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Prescribed analgesics in pregnancy and risk of childhood asthma

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Abstract

Many epidemiological studies have reported a positive association between prenatal exposure to paracetamol and childhood wheezing and asthma. We investigated whether the link between prenatal analgesic exposure and asthma/wheeze is specific to paracetamol, and whether it is causal or confounded.

Using linked Swedish health register data we investigated the relation between various prescribed analgesics in pregnancy and the risk of childhood asthma/wheeze in a population of N=492,999, and used negative paternal control and sibling comparison approaches to explore unmeasured confounding.

After controlling for potential confounders, prescribed opioids, anti-migraine drugs and paracetamol were all positively associated with childhood asthma/wheeze risk at all ages (for example, odds ratios (95% Confidence Intervals) for asthma/wheeze at four years were: 1.39 (1.30-1.49), 1.19 (1.01-1.40) and 1.47 (1.36-1.59), respectively). The results of the paternal control analysis did not suggest the presence of unmeasured confounding by genetics or shared environment However, the sibling comparison analysis broadly suggested that associations between prenatal exposure to the analgesics above and asthma/wheeze were confounded by specific maternal factors (for example, ORs (95% CI) for asthma/wheeze at 4 years were: 0.91 (0.62-1.31), 0.50 (0.17-1.45) and 0.80 (0.50-1.29) for opioids, anti-migraine drugs and paracetamol, respectively).

We propose that analgesic use in pregnancy does not cause childhood asthma/wheeze, and that the association is confounded by unmeasured factors which are intrinsic to the mother, such as chronic pain or anxiety. (225 words)

Key Words: Paracetamol (acetaminophen), opioids, migraine, prenatal, family design

Introduction

Following our original epidemiological observations of a positive association between maternal, self-reported, use of paracetamol (acetaminophen) in pregnancy and risk of preschool wheezing[1], we subsequently reported a positive association with later childhood asthma[2;3]. A number of other birth cohort studies have confirmed these findings[4], and we originally proposed that, if causal, the associations with prenatal exposure might be explained by increased oxidative stress and depletion of glutathione[1-3], however a causal link has not been established. Experimental evidence on effects of prenatal paracetamol in animal models is conflicting[5;6], and a randomised controlled trial to test this hypothesis has not been conducted in humans. Paracetamol is the most commonly used analgesic in pregnancy, so it is important to confirm or refute whether it might be a cause of childhood asthma. Given that a trial in pregnant women would be difficult to undertake[7], there is a need for multiple approaches to rigorously address potential confounding in observational studies.

An important question, relevant to causal inference, is whether the observed epidemiological associations are specific to paracetamol. No association was found with self-reported maternal use of aspirin in pregnancy in our original studies[1;2], nor has there been convincing evidence from other birth cohorts to implicate prenatal exposure to ibuprofen[8-11]. In contrast, a large, population based study from Denmark using linked national registers, reported an increased childhood asthma risk associated with use of prescribed non-steroidal anti-inflammatory drugs, as well as paracetamol[12]. If the relation between maternal analgesic use in pregnancy and childhood asthma risk is not specific to paracetamol, this would suggest, indirectly, that the association may be confounded by indication, rather than causal, since the various implicated analgesics have different modes of action. One study reported an association between maternal pain in pregnancy and childhood asthma risk, in the absence of paracetamol use[9].

Whilst positive epidemiological associations have remained after controlling for measured confounders using conventional multivariate analysis, the possibility of unmeasured confounding cannot be ruled out. One way to investigate this is to use negative parental controls[13;14]; if effect estimates for paternal use during pregnancy are similar to those for maternal use during pregnancy, this would suggest confounding by genetic or shared environmental or lifestyle factors, rather than a direct intrauterine causal effect of prenatal exposure. An alternative family design method, which can be used to assess the possibility of confounding specific to the mother, is sibling control analysis[15]. This approach is based on the principle that siblings share stable aspects of both family environment (prenatal and postnatal) and maternal specific factors (intra-uterine and behavioural), as well as 50% of their segregating genes. Sibling control analysis has not been used previously to investigate the relation between prenatal analgesic exposure and asthma.

We have investigated the association between various prescribed analgesics in pregnancy and the risk of childhood asthma/wheeze using Swedish national health and prescription register data, using negative paternal control and sibling comparisons to address unmeasured confounding.

Methods

Study population

We identified a cohort of children born to women who became pregnant from July 2005 onwards and gave birth before the end of 2010 from the Medical Birth Register (MBR). MBR includes data on maternal, pregnancy and perinatal factors for more than 98% of all births in Sweden. Data were linked, via individual personal identification numbers assigned to all residents in Sweden, to the Migration Register, the Register of the Total Population, the National Patient Register (NPR) and the Swedish Prescribed Drug Register (SPDR). Linkage to the Multi-Generation Register allowed identification of the children's fathers and siblings and the Register of the Total Population dates of death. We accessed data from all registers until December 31, 2013. Children who died or emigrated before the age of outcome were excluded (See online Figure E1).

Exposure

We collected information on prescribed analgesics dispensed during pregnancy from the Swedish Prescribed Drug Register (SPDR). The nationwide SPDR was introduced in July 2005 and contains information on prescription and dispense dates, number of packages and dosage of all prescribed medications dispensed in Swedish pharmacies, based on the Anatomical Therapeutic Chemical (ATC) classification system. Drugs of interest included those included in three analgesic classes, namely, opioids, anti-migraine medication and paracetamol, identified using ATC classification system codes (see online Table E1). Combined preparations of analgesics across the three classes (eg paracetamol plus codeine) were not included, so that we could assess associations with the three classes of analgesics separately. However, a small minority of mothers were prescribed more than one class of analgesic (see online Table E2).

Outcome

Information on childhood asthma was collected from the NPR for all inpatient and specialist outpatient diagnoses (ICD-10: J45 and J46) and from the SPDR for all asthma prescribed medications from both primary and specialist care. Prescriptions were used in a previously validated asthma medication algorithm[16]. In brief, the algorithm for current asthma requires at least one asthma prescription in the last 12 months of either: two or more prescriptions for preventer medications (inhaled corticosteroids (ICS), leukotriene receptor antagonists, ICS combinations) *or* three short-acting beta agonist (SABA) prescriptions *or* two SABA and one preventer medication. Children under 4.5 years were required to fulfil both diagnosis *and* medication criteria in order be more certain that children had asthma rather than preschool wheeze in this age group. Children over 4.5 years were required to have either a diagnosis *or* fulfil medication criteria. These registry based asthma outcomes were objectively assessed and have previously been validated and found to be specific[16]. Nevertheless, as some 'asthma' under 4.5 years of age may actually be preschool wheezing which will not persist as asthma later in childhood, we refer to 'asthma/wheeze' as the outcome being analysed. We defined prevalent asthma/wheeze at 2, 3, 4, 5 and 6 years respectively. Since our dataset included children born 2006-2010, and with administrative censoring of outcome data in December 2013, we have fewer children contributing to the analyses of asthma in the older age groups.

Confounders

We collected information on maternal factors (smoking and body mass index in pregnancy, age at delivery, parity, and country of birth) from the MBR. Paternal country of birth and the highest level of education of either parent were obtained from the Longitudinal Integration Database for Health Insurance and Labour Market Studies. Maternal and paternal asthma

were defined on the basis of dispensed asthma drugs (data from 2005 onwards) or a diagnosis of asthma ever (ICD-8/9: 493; ICD-10: J45, J46) (data from 2001 onwards).

Statistical analysis

Firstly, we used logistic regression to analyse the association between analgesics prescribed to the mother in pregnancy and prevalent childhood asthma/wheeze at ages 2-6 years in the whole cohort (the same individuals could be included at successive ages in the analyses), controlling for the potential maternal confounders listed above. The reference group in all analyses was mothers not prescribed the analgesic being analysed. We analysed prevalent asthma/wheeze separately at each year of age to see whether we observed similar findings for younger children as for older children, given uncertainties over 'asthma' versus preschool wheezing in the younger age groups. We also conducted several sensitivity analyses: (1) In order to increase the likelihood that mothers actually took the prescribed analgesics, we conducted an analysis with analgesic exposure being defined by the drug having been dispensed at least twice during pregnancy. (2) To determine if there was a dose-response effect we analysed whether increasing the number of classes of drugs increased the strength of the association with asthma/wheeze. (3) In case of increased use of over the counter prescriptions, or use of earlier prescriptions in subsequent pregnancies (which could attenuate the findings towards the null), we analysed only those children who were first born.
Secondly, we used logistic regression to analyse the relation between analgesics prescribed to the father during the mother's pregnancy and childhood asthma/wheeze, controlling for potential paternal confounders. We mutually adjusted the paternal analysis for maternal prescription of analgesics in pregnancy and, in turn, mutually adjusted the maternal analysis for paternal prescription of analgesics in pregnancy, because of an observed positive association between maternal and paternal use of analgesics (data not shown).

Thirdly, we used a sibling control design with conditional logistic regression. This design utilises the fact that siblings share family environment (prenatal and postnatal) and maternal specific factors (intra-uterine and behavioural), and adjusts for these unmeasured confounders[17;18]. Siblings also share 50% of the segregating genes. If the association between analgesics and asthma/wheeze in the cohort analysis diminishes, or is attenuated, in the sibling control analysis, it is likely that shared familial factors confound the association. Conversely, if the association remains, then a potential causal explanation is more likely. Controls were all full siblings (excluding children for whom the father's identity was unknown) who did not have asthma, and who were still in the study at the age of the particular analysis (2, 3 or 4 years of age). Analogous to a matched case-control study, only siblings who are discordant for both exposure (analgesics prescribed to the mother) and outcome (asthma) are informative for estimation of effect parameters; asthma at 5 and 6 years of age was excluded as there were too few families with doubly discordant siblings for asthma at these ages. However, potential confounders (factors that are *not* shared between siblings and which are unique for each child) were controlled for.

We also analyzed the data as time to event outcome (incident asthma) using Cox proportional hazards regression in the full cohort of children with an estimated conception date from July 1st 2005 and onwards, who were born before Jan 1st 2013 (N>656,000). This alternative approach was used to confirm or refute the findings from the logistic regression analyses. Date of onset of asthma was defined as the date of the first prescription of asthma medication or diagnosis in the NPR. All children were followed from birth until the earliest of asthma onset, emigration from Sweden, death or Dec 31st 2013. Attained age was used as the analysis timescale. The proportional hazards assumption was tested based on Schoenfield residuals and found to be violated. Therefore a model with time-varying effects was applied, with time-bands ($\leq$ 1 year; > 1 and $\leq$ 2 years; > 2 years) decided based on the data. Results

are presented as hazard ratios (HR) within each time-band with corresponding 95% confidence intervals.

All analyses were performed using Stata, version 13. The study was approved by the regional ethics review board in Stockholm, Sweden.

Results

Table 1 shows maternal characteristics and childhood asthma/wheeze at different ages according to maternal analgesics prescribed in pregnancy. Overall, during pregnancy, 7% of women had a prescription for an analgesic: 4.4% were prescribed opioids, 0.8% were prescribed anti-migraine medications and 3.1% were prescribed paracetamol. The prevalence of childhood asthma/wheeze was 6-7%. After controlling for potential confounders, prescribed opioids, anti-migraine drugs and paracetamol were all positively associated with childhood asthma/wheeze risk at all ages (Table 2, Figure 1 (unadjusted results shown in Table E3)). For example, adjusted odds ratios (95% Confidence Intervals) for asthma/wheeze at four years, were 1.39 (1.30-1.49), 1.19 (1.01-1.40) and 1.47 (1.36-1.59), respectively). Independent associations with each analgesic remained, though attenuated, on mutual adjustment for the other analgesics (Table E4). When we repeated the analyses shown in Table 2, with exposure being defined by the drug having been dispensed at least twice during pregnancy, the effect estimates increased in magnitude (Table E5). With an increasing number of classes of analgesics prescribed to women during pregnancy, the strength of the associations with asthma at ages 2, 3 and 5 increased (Table E6). Including only first born children in the analysis did not change effect estimates (Table E7).

When we analysed the associations between analgesics prescribed to the father and childhood asthma/wheeze, all associations were null (Table 3, Figure 1). For example, adjusted ORs (95% CIs) for asthma/wheeze at four years, were 1.01 (0.93-1.09), 1.12 (0.92-1.37) and 1.03

(0.94-1.13), for opioids, anti-migraine drugs and paracetamol, respectively. Mutually adjusting maternal analyses for paternal use of analgesics during mother's pregnancy did not change the maternal effect estimates (data not shown). In the sibling control analysis, none of the analgesics prescribed to the mother in pregnancy were associated with childhood asthma/wheeze at ages 2, 3 and 4 (for example, adjusted ORs (95% CIs) for asthma/wheeze at four years, were 0.91 (0.62-1.31), 0.50 (0.17-1.45) and 0.80 (0.50-1.29), for opioids, anti-migraine drugs and paracetamol, respectively), with the exception of a positive association between paracetamol and asthma/wheeze at age 3 years (Table 4, Figure 1). This latter association (P=0.014) was no longer conventionally significant after Bonferroni correction. When we used Cox proportional hazards regression the results were in keeping with those of the logistic regression results presented in Tables 2 and 4. In the whole cohort, positive associations with asthma/wheeze were seen with asthma/wheeze incidence for all three analgesic classes (Table E8a); in contrast, in the sibling control analysis, no associations were seen for any of the analgesics (Table E8b).

Discussion

In this large population-based study we found that, after controlling for measured confounders, various prescribed analgesics, including opioids, anti-migraine drugs and paracetamol in pregnancy were associated with an increased risk of childhood asthma/wheeze. These associations were stronger when the analgesics had been dispensed twice or more during pregnancy. Whilst the findings for paracetamol, including prescribed paracetamol, are not new[4;12], to our knowledge, only one previous study has suggested that prescribed opioids may also be associated with childhood asthma risk[11]; that study found an association with prescribed anti-migraine drugs in pregnancy of borderline significance. Our findings were consistent whether we analysed prevalent or incident asthma/wheeze.

Investigation of confounding

We used two approaches to investigate whether the associations between prenatal exposure to analgesics and childhood asthma/wheeze might be explained by unmeasured confounding. First, we used a negative paternal control approach. We found no association between paternal analgesic use and childhood asthma/wheeze, which is in keeping with two previous studies[9;19], and suggests that the maternal analgesic-asthma/wheeze associations were not confounded by unmeasured genetic, environmental, socioeconomic or lifestyle factors shared by the mother and father, which might influence both the propensity for taking prescribed analgesics and the risk of asthma in the offspring. However, we also used a sibling comparison approach, which to our knowledge has not been used previously to test this hypothesis. This showed that the three classes of analgesic were not associated with asthma/wheeze at 2, 3 and 4 years, with one exception – paracetamol was associated with asthma/wheeze at 3 years; whilst the latter association may be a chance finding, we cannot rule out a causal association. However, the predominant lack of association across the sibling

control analyses (which was corroborated when we analysed incident asthma/wheeze using Cox regression) suggests that a large causal effect of maternal analgesic use on risk of childhood asthma/wheeze is unlikely, since the sibling exposed to the maternal use of analgesics had no higher risk of the asthma/wheeze outcomes than the unexposed sibling (although we acknowledge that, given the wide confidence limits, a small/modest effect cannot be ruled out). This suggests that, although the paternal negative control analysis ruled out confounding by unmeasured genetic factors or shared environment, the sibling analysis indicate possible confounding of the associations between prenatal analgesic exposure and asthma/wheeze by unmeasured factors, which are intrinsic to the mother, and may be common to successive pregnancies. We speculate that these might include a physiological condition such as chronic pain or anxiety, or a behavioural trait such as a propensity to seek health care. Confirmation that the relation between prenatal analgesic exposure and asthma/wheeze was not restricted to paracetamol also supports confounding by a stable factor intrinsic to the mother as a likely explanation, given that the three types of analgesic have different mechanisms of action. In regards to chronic pain as a possible maternal confounder, a recent birth cohort study found some evidence that maternal pain, in the absence of paracetamol use, was associated with an increased risk of childhood asthma[9]. Anxiety has been linked to increased prescribed opioid use in pregnancy[20], and anxiety can exacerbate pain sensation[21]. Maternal psychological stress, in turn, has been linked to childhood asthma risk[22], so could potentially be a confounder, although previous studies have shown that the association between prenatal paracetamol exposure and asthma remains after adjusting for maternal anxiety[1-3].

Strengths and limitations

Aside from its large size, our study has a number of important strengths. First, the linkage of national registers using objectively and prospectively collected measures of exposure and validated outcomes[16], which enables virtually complete coverage and follow-up of the Swedish population, thus reducing the risk of selection and recall bias which can arise in birth cohort studies. Second, the use of negative control analysis and the novel use of sibling control analysis to address unmeasured familial confounding. Third, whether we analysed prevalent asthma/wheeze using logistic regression or incident asthma/wheeze using Cox proportional hazards regression, the results for the whole cohort and in the sibling control analyses were similar.

A limitation of our dataset is that we had fewer children contributing to the analyses of asthma in the older age groups, and especially in the sibling control analysis. A future study, designed to capture a larger number of children with asthma at older ages, could be informative. Regarding other potential limitations, whilst we analysed prescribed paracetamol, this drug is also readily obtained over the counter (OTC), which could potentially lead to misclassification of exposure to this drug. However, in Sweden, paracetamol is only available OTC in smaller doses and package sizes for a relative increased cost, and therefore it is more likely to be used sporadically rather than for long term use; individuals needing frequent use tend to get the drug prescribed as this is cheaper. Furthermore, any exposure misclassification is likely to be random with respect to childhood asthma/wheeze and this would be expected to lead to underestimation of effect estimates (as would any exposure misclassification arising from mothers not actually taking analgesics that they had been prescribed, although we at least know that the prescribed drugs were dispensed). In contrast, opioids such as codeine, dextropropoxyphene, and tramadol, and anti-migraine drugs, cannot be obtained OTC in Sweden, and therefore the results for these

analgesics could be regarded as more convincing, as exposure misclassification will be minimal. Reduced exposure misclassification might also explain why we observed stronger associations when exposure was defined by the drug having been dispensed at least twice in pregnancy, as we can be more confident that exposed mothers actually took the drug during pregnancy. Given the likely sporadic use of OTC paracetamol, we think it unlikely that minor usage of OTC paracetamol use will have confounded the associations seen with codeine and anti-migraine drugs.

Whilst a proportion of children under 5 years with a hospital diagnosis of asthma and receiving asthma medication may have had preschool wheezing, our analyses are still valid, as previous epidemiological studies have linked prenatal paracetamol exposure to early childhood wheezing[1], as well as to later asthma[2;3].

Conclusions

In summary, our findings confirm that analgesic use in pregnancy is associated with an increased risk of childhood asthma/wheeze, but this link is not specific to paracetamol, and is unlikely to be causal. We posit that factors intrinsic to the mother and common across pregnancies, such as chronic pain or anxiety, may be confounding the prenatal analgesic-asthma/wheeze association. There have been previous calls for placebo controlled trials to definitively test the paracetamol-asthma hypothesis[23]. We would argue, on the basis of our latest findings, that the case for a trial in pregnancy, which would present considerable practical and ethical challenges, is now less strong.

Competing interests

None of the authors have any conflicts of interests to declare.

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Contributors

SOS and CA conceived the project. CL and BKB carried out the statistical analyses. SOS drafted the manuscript and all authors contributed to, and approved, the final version.

Table 1. Maternal characteristics and asthma/wheeze in the child, overall and by maternal analgesics prescribed in pregnancy

	All N=492 999		Opioids N=21 650		Anti-migraine N=3 722		Paracetamol N=14 732	
	n	(%)	N	(%)	n	(%)	n	(%)
Maternal characteristics								
Birth country								
Sweden	392 886	(79.7)	17 409	(80.4)	3 212	(86.3)	9 867	(67.0)
Nordic (not Sweden)	6 917	(1.4)	336	(1.6)	50	(1.3)	208	(1.4)
EU	12 829	(2.6)	431	(2.0)	76	(2.0)	324	(2.2)
Europe (not EU)	18 718	(3.8)	720	(3.3)	85	(2.3)	834	(5.7)
Africa	13 475	(2.7)	597	(2.8)	43	(1.2)	697	(4.7)
North America	1 829	(0.4)	100	(0.5)	7	(0.2)	47	(0.3)
South America	5 249	(1.1)	295	(1.4)	36	(1.0)	173	(1.2)
Asia	40 615	(8.2)	1 737	(8.0)	207	(5.6)	2 571	(17.5)
Oceania	207	(0.0)	12	(0.1)	2	(0.1)	5	(0.0)
Soviet Union	221	(0.0)	13	(0.1)	4	(0.1)	4	(0.0)
Missing	53	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Education								
Elementary school (9 years)	23 792	(5.1)	1 316	(6.1)	125	(3.4)	1 489	(10.1)
Secondary school (11-12 years)	181 288	(36.8)	9 469	(43.7)	1 334	(35.8)	6 442	(43.7)
College/university	286 456	(58.1)	10 827	(50.0)	2 262	(60.8)	6 739	(45.7)
Missing	1 463	(0.3)	38	(0.2)	1	(0.0)	62	(0.4)
Asthma								
No	428 771	(87.0)	16 697	(77.1)	2 909	(78.2)	11 033	(74.9)
Yes	64 228	(13.0)	4 953	(22.9)	813	(21.8)	3 699	(25.1)
BMI in early pregnancy								
<18.5	10 741	(2.2)	403	(1.9)	58	(1.6)	251	(1.7)
18.5-24.9	275 170	(55.8)	10 112	(46.7)	1 854	(49.8)	6 268	(42.5)
25-29.9	111 321	(22.6)	5 529	(25.5)	939	(25.2)	4 013	(27.2)
≥ 30	53 990	(11.0)	3 633	(16.8)	542	(14.6)	2 973	(20.2)
Missing	41 777	(8.5)	1 973	(9.1)	329	(8.8)	1 227	(8.3)
Parity								
1	216 556	(43.9)	8 223	(38.0)	1 603	(43.1)	5 112	(34.7)
2	181 265	(36.8)	7 714	(35.6)	1 254	(33.7)	4 846	(32.9)
3	66 898	(13.6)	3 678	(17.0)	574	(15.4)	2 707	(18.4)
≥ 4	28 280	(5.7)	2 035	(9.4)	291	(7.8)	2 067	(14.3)
Smoking during pregnancy								
No	493 338	(89.1)	18 123	(83.7)	3 310	(88.9)	12 507	(84.9)
Yes	32 757	(6.6)	2 561	(11.8)	252	(6.8)	1 664	(11.3)
Missing	20 904	(4.2)	966	(4.5)	160	(4.3)	561	(3.8)

Maternal age at delivery								
< 20	7 760	(1.6)	215	(1.0)	14	(0.4)	149	(1.0)
20-24	62 013	(12.6)	2 578	(11.9)	256	(6.9)	1 696	(11.5)
25-29	140 780	(28.6)	5 888	(27.2)	833	(22.4)	3 776	(25.6)
30-34	173 400	(35.2)	7466	(34.5)	1 405	(37.7)	4 893	(33.2)
35-40	90 031	(18.3)	4 445	(20.5)	965	(25.9)	3 235	(22.0)
≥ 40	19 015	(3.9)	1 058	(4.9)	249	(6.7)	983	(6.7)
Childhood asthma/wheeze								
At age 2 yrs								
Yes	35 708	(7.2)	2492	(11.5)	388	(10.4)	1 701	(11.5)
Total N=492,999								
At age 3 yrs								
Yes	27 876	(7.3)	1 851	(11.4)	305	(10.9)	9 610	(11.9)
Total N=381,729								
At age 4 yrs								
Yes	19 761	(7.2)	1 220	(10.6)	193	(9.8)	852	(11.1)
Total N=276,333								
At age 5 yrs								
Yes	11 849	(6.8)	732	(10.3)	134	(11.3)	507	(10.8)
Total N=173,131								
At age 6 yrs								
Yes	4 451	(6.1)	290	(9.5)	51	(10.3)	194	(9.9)
Total N=72,778								

Table 2. Associations between prescribed analgesics in pregnancy and childhood asthma/wheeze (whole cohort)

Asthma/wheeze		Opioids		Anti-migraine		Paracetamol	
Age (years)	n	OR[1]	(95% CI)	OR[1]	(95% CI)	OR[1]	(95% CI)
2	449 934	1.48	(1.42-1.55)	1.31	(1.17-1.47)	1.51	(1.43-1.60)
3	346 223	1.47	(1.39-1.55)	1.37	(1.20-1.56)	1.58	(1.48-1.68)
4	248 785	1.39	(1.30-1.49)	1.19	(1.01-1.40)	1.47	(1.36-1.59)
5	152 797	1.42	(1.30-1.55)	1.48	(1.21-1.80)	1.50	(1.35-1.66)
6	64 642	1.39	(1.21-1.59)	1.41	(1.02-1.96)	1.46	(1.23-1.72)

[1] Odds ratio adjusted for maternal birth country, education, asthma, BMI in early pregnancy, parity, smoking during pregnancy and age at delivery

Figure 1: Associations between prescribed analgesics in pregnancy and childhood asthma/wheeze: whole cohort, negative control and sibling control analyses

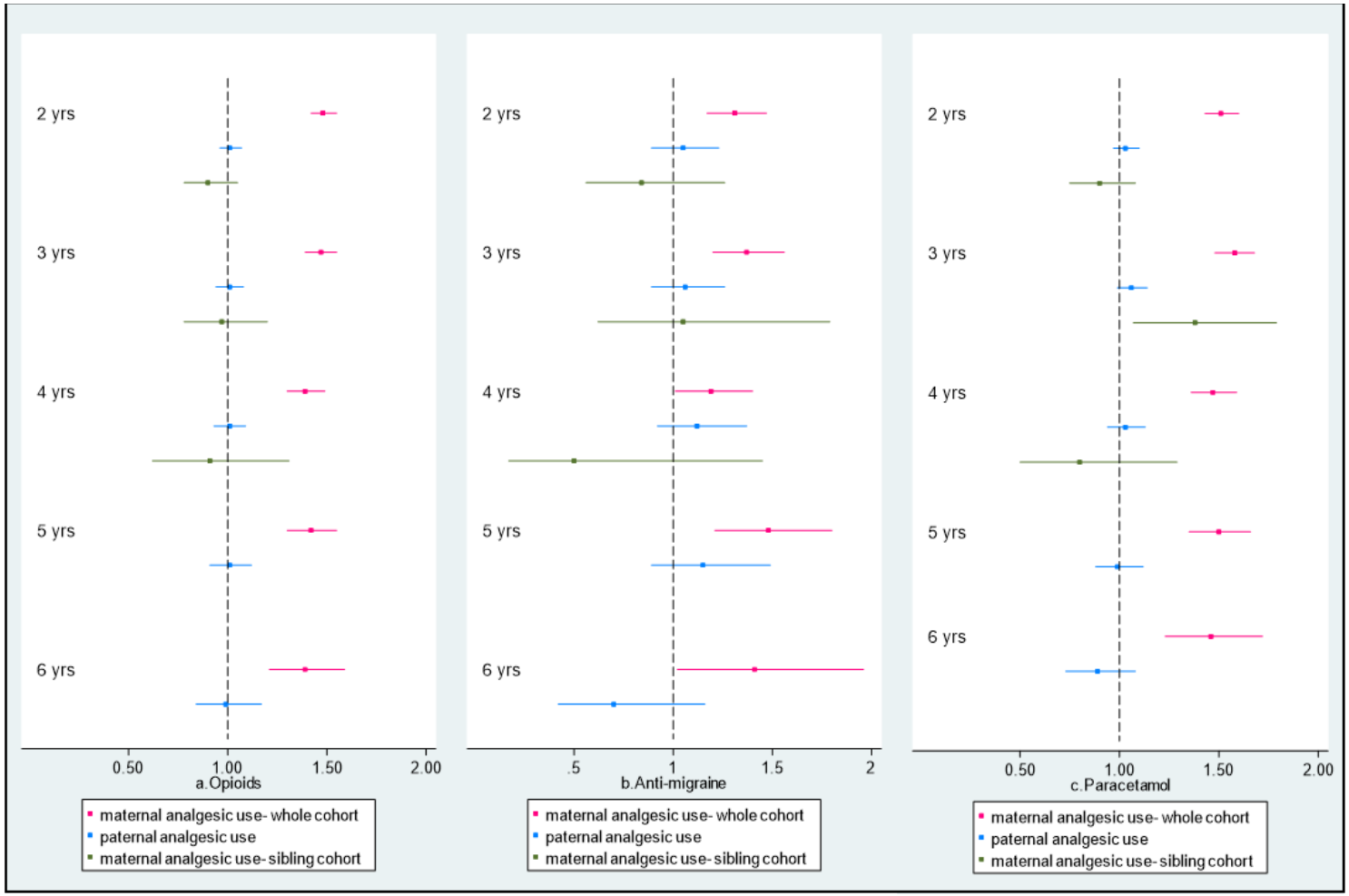

Table 3: Negative Control Analysis.

Paternal analgesic prescription during mother's pregnancy and childhood asthma/wheeze							
Asthma/wheeze		Opioids		Anti-migraine		Paracetamol	
Age (years)	n	OR[1]	(95% CI)	OR[1]	(95% CI)	OR[1]	(95% CI)
2	445 726	1.01	(0.96, 1.07)	1.05	(0.89, 1.23)	1.03	(0.97, 1.10)
3	348 335	1.01	(0.94, 1.08)	1.06	(0.89, 1.26)	1.06	(0.99, 1.14)
4	246 912	1.01	(0.93, 1.09)	1.12	(0.92, 1.37)	1.03	(0.94, 1.13)
5	152 797	1.01	(0.91, 1.12)	1.15	(0.89, 1.49)	0.99	(0.88, 1.12)
6	64 229	0.99	(0.84, 1.17)	0.70	(0.42, 1.16)	0.89	(0.73, 1.08)

[1] Odds ratio adjusted for paternal birth country, education, paternal asthma, parity, maternal asthma, maternal birth country, BMI in early pregnancy, smoking during pregnancy, maternal age at delivery, maternal analgesic prescription during pregnancy

Table 4: Associations between analgesics prescribed to the mother in pregnancy and childhood asthma/wheeze: sibling comparison analysis

Asthma /wheeze			**Opioids**			**Anti-migraine**			**Paracetamol**	
Age (years)	n[1]		OR[2]	(95% CI)		OR[2]	(95% CI)		OR[2]	(95% CI)
2	17 522		0.90	(0.78-1.05)		0.84	(0.56-1.26)		0.90	(0.75-1.08)
3	9 456		0.97	(0.78-1.20)		1.05	(0.62-1.79)		1.38	(1.07-1.79)
4	3 764		0.91	(0.62-1.31)		0.50	(0.17-1.45)		0.80	(0.50-1.29)

[1] Number of children in families with siblings doubly discordant for asthma and exposures

[2] Odds ratio adjusted for maternal BMI in early pregnancy, parity, smoking during pregnancy and age at delivery

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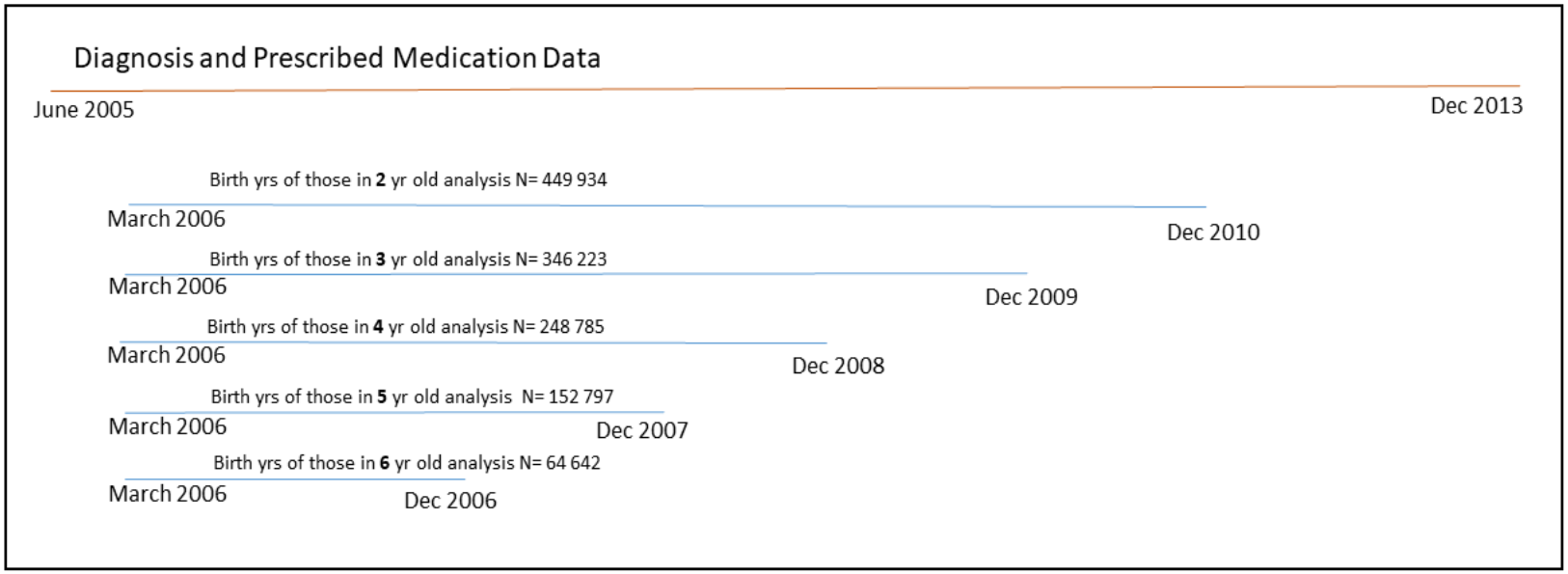
Online data supplement

Figure E1: Data available for analysis



Footnote: Numbers refer to adjusted analyses (complete data on covariates)

Table E1. Three classes of analgesics included in the analyses

	ATC codes	Generic drug name
Opioids	N02AA59	Codeine, combinations excluding psycholeptics
	N02AA79	Codeine, combinations with psycholeptics
	N02AA08	Dihydrocodeine
	N02AA58	Dihydrocodeine, combinations
	N02AC04	Dextropropoxyphene
	N02AC54	Dextropropoxyphene, combinations excluding psycholeptics
	N02AX02	Tramadol
Anti-migraine	N02CA01	Dihydroergotamine
	N02CA02	Ergotamine
	N02CA04	Methysergide
	N02CA07	Lisuride
	N02CA51	Dihydroergotamine, combinations
	N02CA52	Ergotamine, combinations excluding psycholeptics
	N02CA72	Ergotamine, combinations with psycholeptics
	N02CC01	Sumatriptan
	N02CC02	Naratriptan
	N02CC03	Zolmitriptan
	N02CC04	Rizatriptan
	N02CC05	Almotriptan
	N02CC06	Eletriptan
	N02CC07	Frovatriptan
	N02CX01	Pizotifen
	N02CX02	Clonidine
	N02CX03	Iprazochrome
	N02CX05	Dimetotiazine
	N02CX06	Oxetorone
	N02CB01	Flumedroxone
Paracetamol	N02BE01	Paracetamol
	N02BE51	Paracetamol, combinations excluding psycholeptics
	N02BE71	Paracetamol, combinations with psycholeptics

Table E2. Frequency of analgesic classes prescribed to the mother during pregnancy

Opioids	Anti-migraine	Paracetamol	N	%
No	No	No	459,690	93.2
No	No	Yes	9,091	1.8
Yes	No	No	15,405	3.1
No	Yes	No	2,343	0.5
Yes	No	Yes	5,091	1.0
No	Yes	Yes	225	0.0
Yes	Yes	No	829	0.2
Yes	Yes	Yes	325	0.1

Table E3. Associations between prescribed analgesics in pregnancy and childhood asthma/wheeze (whole cohort; unadjusted analysis)

Asthma/wheeze		Opioids		Anti-migraine		Paracetamol	
Age (years)	n	OR[1]	(95% CI)	OR[1]	(95% CI)	OR[1]	(95% CI)
2	492, 999	1.72	(1.64, 1.79)	1.50	(1.34, 1.67)	1.71	(1.62, 1.80)
3	381 729	1.67	(1.59, 1.76)	1.55	(1.37, 1.75)	1.75	(1.65, 1.86)
4	276 333	1.58	(1.49, 1.68)	1.42	(1.22, 1.65)	1.65	(1.54, 1.78)
5	173 131	1.61	(1.48, 1.74)	1.74	(1.45, 2.09)	1.67	(1.52, 1.83)
6	72 778	1.65	(1.45, 1.87)	1.78	(1.32, 2.39)	1.71	(1.48, 2.00)

Table E4. Associations between prescribed analgesics in pregnancy and childhood asthma/wheeze (whole cohort), mutually adjusted for the other analgesics

Asthma/ wheeze		Opioids		Anti-migraine		Paracetamol	
Age (years)	n	OR[1]	(95% CI)	OR[1]	(95% CI)	OR[1]	(95% CI)
2	449 934	1.37	(1.30-1.44)	1.15	(1.03-1.30)	1.34	(1.26-1.43)
3	346 223	1.33	(1.26-1.41)	1.21	(1.06-1.38)	1.41	(1.32-1.51)
4	248 785	1.29	(1.20-1.38)	1.07	(0.91-1.27)	1.34	(1.24-1.36)
5	152 797	1.30	(1.18-1.42)	1.34	(1.09-1.65)	1.36	(1.21-1.51)
6	64 642	1.28	(1.11-1.49)	1.27	(0.90-1.80)	1.33	(1.11-1.58)

[1] Odds ratio adjusted for maternal birth country, education, asthma, BMI in early pregnancy, parity, smoking during pregnancy, age at delivery and **mutual adjustment for the other analgesics**

Table E5. Associations between prescribed analgesics in pregnancy and childhood asthma/wheeze (whole cohort), with exposure being defined by the drug having been dispensed at least twice during pregnancy

Asthma/wheeze		Opioids		Anti-migraine		Paracetamol	
Age (years)	n	OR[1]	(95% CI)	OR[1]	(95% CI)	OR[1]	(95% CI)
2	449 934	1.57	(1.44-1.71)	1.39	(1.16-1.67)	1.61	(1.47-1.76)
3	346 223	1.59	(1.44-1.75)	1.39	(1.12-1.72)	1.70	(1.54-1.89)
4	248 785	1.50	(1.34-1.70)	1.29	(0.99-1.68)	1.68	(1.48-1.91)
5	152 797	1.47	(1.26-1.72)	1.60	(1.16-2.22)	1.61	(1.35-1.90)
6	64 642	1.54	(1.22-1.96)	1.18	(0.65-2.15)	1.68	(1.29-2.18)

[1] Odds ratio adjusted for maternal birth country, education, asthma, BMI in early pregnancy, parity, smoking during pregnancy and age at delivery

Table E6. Odds ratios (OR) and 95% confidence intervals (CI) from logistic regression of asthma/wheeze at age 2-6 years by number of classes of analgesic drugs (opioids, anti-migraine, paracetamol)

		Number of classes of analgesics					
Asthma/ wheeze		One		Two		Three	
Age (years)	n	OR[1]	(95% CI)	OR[1]	(95% CI)	OR[1]	(95% CI)
2	449 934	1.42	(1.36-1.48)	1.67	(1.54-1.81)	1.69	(1.21-2.36)
3	346 223	1.42	(1.35-1.49)	1.61	(1.44-1.81)	2.00	(1.38-2.90)
4	248 785	1.34	(1.26-1.42)	1.39	(1.30-1.49)	1.28	(0.74-2.19)
5	152 797	1.36	(1.26-1.48)	1.69	(1.45-1.28)	1.94	(1.03-3.68)
6	64 642	1.36	(1.19-1.55)	1.62	(1.27-2.06)	1.36	(0.41-4.52)

[1] Adjusted for maternal birth country, education, asthma, BMI in early pregnancy, parity, smoking during pregnancy and age at delivery

Table E7. Associations between prescribed analgesics in pregnancy and childhood asthma/wheeze (first born children only)

Asthma/wheeze		Opioids		Anti-migraine		Paracetamol	
Age (years)	n	OR[1]	(95% CI)	OR[1]	(95% CI)	OR[1]	(95% CI)
2	197 505	1.48	(1.37, 1.60)	1.27	(1.07, 1.52)	1.51	(1.37-1.66)
3	152 056	1.39	(1.27, 1.52)	1.40	(1.16, 1.70)	1.55	(1.39, 1.72)
4	109, 104	1.32	(1.19, 1.47)	1.32	(1.05, 1.67)	1.45	(1.28, 1.66)
5	66 552	1.41	(1.23, 1.62)	1.51	(1.12, 2.03)	1.48	(1.25, 1.75)
6	28 156	1.45	(1.17, 1.80)	1.40	(0.85, 2.31)	1.54	(1.18, 2.02)

[1] Odds ratio adjusted for maternal birth country, education, asthma, BMI in early pregnancy, smoking during pregnancy and age at delivery

Table E8: Age-varying hazard ratios (HR) from Cox proportional hazards regression of association between incident maternal analgesic prescription and asthma/wheeze incidence

a. HRs adjusted for measured confounders[1] (n=656,440, events=55,761)

Age band	Opioids		Anti-migraine		Paracetamol	
(years)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
0-1	1.52	(1.44, 1.60)	1.32	(1.16, 1.51)	1.57	(1.48, 1.67)
1-2	1.46	(1.38, 1.55)	1.27	(1.10, 1.46)	1.37	(1.28, 1.47)
>2	1.35	(1.26, 1.44)	1.44	(1.25, 1.67)	1.37	(1.27, 1.48)

b. Sibling comparison: HRs adjusted for factors shared by siblings, using stratified models, and measured confounders not shared by siblings[2] (n=658,898, events=55,990)

Age band	Opioids		Anti-migraine		Paracetamol	
(years)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
0-1	1.10	(0.97, 1.27)	1.28	(0.90, 1.82)	1.11	(0.95, 1.29)
1-2	0.96	(0.81, 1.14)	0.70	(0.45, 1.11)	1.03	(0.84, 1.27)
>2	0.94	(0.73, 1.21)	1.12	(0.59, 2.13)	0.88	(0.64, 1.21)

[1] maternal birth country, education, asthma, BMI in early pregnancy, parity, smoking during pregnancy and age at delivery

[2] BMI in early pregnancy, parity, smoking during pregnancy and age at delivery