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Prenatal and Infant Paracetamol Exposure and Development of Asthma: the Norwegian Mother and Child Cohort Study

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Key messages:

- Prenatal and infant paracetamol exposure was independently associated with asthma development after adjusting for common indications.
- We compared associations between several conditions during pregnancy, with and without the use of paracetamol, and asthma development in the offspring. Our findings suggest that the associations could not be fully explained by confounding by indication.
- Maternal use of paracetamol outside of pregnancy and paternal use of paracetamol did not show associations with asthma development in the offspring, indicating little influence by unmeasured characteristics reflected in the propensity for using paracetamol.

Abstract

Background: Paracetamol exposure has been positively associated with asthma development. The relative importance of prenatal versus infant exposure and confounding by indication remains elusive. We examined the association of prenatal and infant (first 6 months) paracetamol exposure with asthma development while addressing confounding by indication.

Methods: We used information from the Norwegian Mother and Child Cohort Study, including 53,169 children for evaluation of current asthma at 3 years, 25,394 for current asthma at 7 years, and 45,607 for dispensed asthma medications at 7 years in the Norwegian Prescription Database. We calculated adjusted relative risks (adj.RR) and 95% confidence intervals (CI) using log-binomial regression.

Results: There were independent modest associations between asthma at 3 years with prenatal paracetamol exposure (adj.RR 1.13; 95 % CI: 1.02-1.25) and use of paracetamol during infancy (adj.RR 1.29; 95% CI: 1.16-1.45). The results were consistent for asthma at 7 years. The associations with prenatal paracetamol exposure were seen for different indications (pain, respiratory tract infections/influenza and fever). Maternal pain during pregnancy was the only indication that showed an association both with and without paracetamol use. Maternal paracetamol use outside of pregnancy or paternal paracetamol use was not associated with asthma development. In a secondary analysis, prenatal ibuprofen exposure was positively associated with asthma at 3 years but not asthma at 7 years.

Conclusions: This study provides evidence that prenatal and infant paracetamol exposure have independent associations with asthma development. Our findings provided suggest that the associations could not be fully explained by confounding by indication.

Introduction

Asthma is the most common chronic disease during childhood.(1, 2) Prenatal and infant paracetamol exposure is proposed to be positively associated with asthma.(3-5) However, few previous studies were able to evaluate the relative importance of prenatal versus infant paracetamol exposure.(6-8) Paracetamol is the recommended analgesic/antipyretic for pregnant women and infants.(9) If the observed associations reflect true underlying effects, this is a public health concern. A limited number of previous studies of prenatal paracetamol exposure and asthma development considered confounding by indication.(7, 10, 11)

An inherent limitation in observational studies is the possibility of unmeasured confounding. One approach to examine whether associations in observational studies might reflect unmeasured characteristics influencing the propensity for exposure is to use negative controls.(12, 13) Examples of negative controls include maternal use of paracetamol outside of pregnancy and the father's use of paracetamol. If the associations are similar for maternal paracetamol use outside of pregnancy and paternal paracetamol use, it is likely that confounding by genetic or shared environmental characteristics is present.(12, 13)

The objective of the study was thus to examine the association of prenatal and infant paracetamol exposure with asthma development while addressing confounding by indication. To further assess whether the previously reported associations reflected unmeasured confounding, we evaluated maternal paracetamol use outside of pregnancy and paternal paracetamol use. Since ibuprofen is used for many of the same indications as paracetamol, we also evaluated the association between prenatal ibuprofen exposure and asthma development.

Methods

Study population

We used data from the Norwegian Mother and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health.(14, 15) MoBa recruited pregnant women between 1999 and 2008, at approximately 18 weeks gestation. The participation rate of invited pregnant women was 40.6%. Mothers could participate with more than one pregnancy, resulting in approximately 95,200 mothers and 114,500 children. All participants gave a written informed consent. In May 2014, the 114,761 children participating in MoBa were linked to the Medical Birth Registry of Norway (henceforth called "birth registry") and the Norwegian Prescription Database (henceforth called "prescription registry"). Children not linked to the birth registry (n=499) and children from multiple births (n=3,971) were not eligible for the current study. We used information from the MoBa questionnaires completed at 18 and 30 gestational weeks, and when the child was 6 months, 3 years and 7 years. The Norwegian Data Inspectorate and the Regional Ethics Committee for Medical Research of South/East Norway approved this study.

Exposures

Participating mothers reported the use of medications for different indications during pregnancy through questionnaires completed at 18 gestational weeks, 30 gestational weeks and when the child was 6 months old. The mother was asked if she had experienced the disease/symptom of interest, and to list the medications she had used for that specific disease/symptom. The mother also listed the child's use of medications during the first 6 months of life. Medications were coded using the Anatomical Therapeutic Chemical classification system (ATC). Medications containing paracetamol (N02BE01, N02AA59, N02AX52 and N02BE51) were extracted. Three of the medications contained other active

ingredients, namely codeine (N02AA59), tramadol (N02AX52) and caffeine (N02BE51). To distinguish between prenatal versus infant paracetamol exposure, we classified mutually exclusive exposure categories: no exposure, prenatal exposure only, infant exposure only, both prenatal and infant exposure.

Outcomes

We examined two asthma outcomes based on the MoBa questionnaires and one outcome based on dispensed asthma medications: 1) We defined current asthma at 3 years as a "yes" in response to current asthma in combination with use of short- or long-acting beta (2)-agonists (R03AC) and/or inhaled corticosteroids (R03BA) in the past year reported in the 3 year questionnaire. 2) Current asthma at 7 years was defined according to three positive criteria reported in the 7 year questionnaire: a positive report of ever asthma, experiencing asthma symptoms the past year and using medications for asthma in the past year. 3) A separate asthma definition at age 7 was based on information from the prescription registry. A child was regarded as having asthma if he/she had a dispensed asthma medication during the past year in addition to a second dispensed prescription within one year after the first. Asthma medications included R03AC, R03BA, R03AK, and R03DC.

Other variables

Maternal characteristics included age, parity, education, pre-pregnancy body mass index (weight in kilograms divided by measured height in meters squared), smoking during pregnancy, asthma, respiratory tract infections/influenza during pregnancy, pain during pregnancy, fever during pregnancy and use of antibiotics during pregnancy. Child characteristics included the child's gender, birth weight, breastfeeding the first 6 months, respiratory tract infections the first 6 months, body mass index at 6 months and use of

antibiotics the first 6 months. We classified antibiotics for systemic use based on ATC codes J01A-J01X.

Statistical analyses

The analysis consisted of several steps. First, we examined the associations between prenatal and infant paracetamol exposure with asthma development using log-linear regression, reporting relative risks (RR) and 95% confidence intervals (CI). The multivariable analyses adjusted for all the potential confounding factors in Table 1. We used cluster variance estimation to account for siblings in the analyses. In order to evaluate whether maternal history of asthma was an effect modifier on the multiplicative scale, we included product terms in the multivariable regression models.

Secondly, we evaluated the likelihood of confounding by indication by focusing on three common indications for use of paracetamol in pregnancy: pain, fever and respiratory tract infections/influenza. There was little a priori evidence that maternal pain during pregnancy might be associated with asthma development in the offspring. However, we wanted to evaluate whether maternal use of paracetamol for different/partly unrelated indications yielded similar associations with asthma development in the offspring. We categorized mutually exclusive exposure categories of mothers who had experienced the different indications with and without the use of paracetamol. In order to evaluate whether these maternal indications acted as effect modifiers on the multiplicative scale, we included product terms in the multivariable regression models. Third, we conducted sensitivity analyses to explore unmeasured confounding by background factors influencing the propensity of paracetamol exposure by examining maternal use of paracetamol the last 6 months before pregnancy, maternal use of paracetamol the first 6 months after pregnancy and the father's paracetamol use.

Fourth, since paracetamol and ibuprofen are used for similar indications, information about maternal use of ibuprofen during pregnancy was extracted (M01AE01). We subsequently evaluated prenatal exposure to paracetamol and ibuprofen in combination (neither, only ibuprofen, only paracetamol, both ibuprofen and paracetamol), to evaluate whether maternal use of these two medications during pregnancy yielded the same association with asthma development.

There were approximately 10-15% of observations with missing information in the multivariable analyses. We therefore conducted multiple imputation by chained equations, imputing a total of 20 datasets.

All of the p-values presented are two-sided. We conducted the analyses using Stata version 13 (Statacorp, Texas).

Results

A total of 53,169 children were included in the analysis of current asthma at 3 years, 25,394 in the evaluation of current asthma at 7 years, and 45,607 in the evaluation of dispensed asthma medications at 7 years (Figure 1). The characteristics among individuals with and without the necessary follow-up information are given in Supplementary Table 1. A total of 27.9% of children were only exposed to paracetamol during pregnancy, 15.5% only during infancy, while 19.1% were exposed both during pregnancy and infancy. The distribution of characteristics by prenatal and infant paracetamol exposure is given in Table 1 (Table 1 here).

A total 5.7% of children had current asthma at 3 years, 5.1% had current asthma at 7 years while 4.8% had dispensed asthma medications at 7 years. There were independent associations between asthma at 3 years with prenatal paracetamol exposure (adj.RR 1.13; 95 % CI: 1.02-1.25) and use of paracetamol during infancy (adj.RR 1.29; 95% CI: 1.16-1.45) (Table 2) (Table 2 here). Similar results were observed for current asthma at 7 years and dispensed asthma medications at 7 years (Table 2).

There was no strong evidence of multiplicative interaction between prenatal and infant paracetamol exposure on asthma development (p-values $_{\text{interaction}}$ >0.07). Separate analyses of prenatal and infant paracetamol exposure with asthma development are included in Supplementary Table 2. The results indicated a slightly stronger association between children exposed to paracetamol during two time periods of pregnancy with asthma development (Supplementary Table 2).

Our findings indicated evidence of an interaction by maternal history of asthma on the association between infant paracetamol exposure and asthma at 3 years (p-value $_{\text{interaction}}$ <0.01) (Supplementary Table 3). However, there was no strong evidence of an interaction by maternal history of asthma for the association between prenatal paracetamol and asthma

development, or the association between infant paracetamol exposure and the asthma outcomes at 7 years (p-values $_{interaction}$ > 0.1) (Supplementary Table 3).

We evaluated respiratory tract infections/influenza, fever and pain during pregnancy as common indications for using paracetamol. Prenatal paracetamol exposure for these three indications yielded similar associations with asthma development (Table 3) (Table 3 here). Furthermore, pain showed a positive association with asthma development without the use of paracetamol (Table 3). The strongest association was seen if the mother used paracetamol during pregnancy for more than one indication, adj.RR 1.94 (95% CI: 1.58-2.37) for current asthma at 3 years (Table 3). In order to further evaluate the potential role of confounding by indication, we conducted stratified analyses of the association between prenatal paracetamol exposure and asthma development by the three indications in turn (Supplementary Table 4). The results indicated no strong evidence of multiplicative interaction (p-values $_{interaction}$ >0.3). Likewise, we also conducted a stratified analysis of the association between infant paracetamol exposure and asthma development by the child's experience of respiratory tract infections the first 6 months of life (Supplementary Table 5). The results indicated no evidence of multiplicative interaction (p-values $_{interaction}$ >0.5). There was no strong evidence of an association between paternal paracetamol use and asthma in the offspring (Supplementary Table 6). Likewise, maternal paracetamol use during the last 6 months before pregnancy, or the first 6 months after delivery, showed no strong evidence of an association with asthma in the offspring (Supplementary Table 6).

Prenatal exposure to ibuprofen was only reported for 5.8% of children. Prenatal exposure to ibuprofen only (no exposure to paracetamol) showed some evidence of an association with current asthma at 3 years, adj.RR 1.31 (95% CI: 1.00,1.72), while there was weak evidence for a positive association with current asthma at 7 years and dispensed asthma medications at 7 years (Table 4) (Table 4 here).

The results from the multiple imputation analyses were similar to the complete case analyses (Supplementary Table 7). A sensitivity analysis of prenatal paracetamol exposure excluding mothers who had reported multiple medications and indicated multiple time periods (during and outside of pregnancy), approximately 9% of mothers, also indicated similar associations (data not shown).

Discussion

This large-scale prospective observational study indicated that both prenatal and infant paracetamol exposure showed independent positive associations with asthma development. Furthermore, the association between prenatal paracetamol exposure and asthma development was similar if used for respiratory tract infections/influenza, fever or pain. Prenatal ibuprofen exposure was only associated with an early asthma phenotype.

Comparison with previous studies

Our finding that prenatal and infant paracetamol exposure is positively associated with asthma development is largely in accordance with results summarized in meta-analyses.(3-5) However, most studies in these meta-analyses did not address confounding by indication.

Of the three previous studies examining prenatal paracetamol exposure and asthma development that adjusted for infections/antibiotics during pregnancy, all reported a positive association.(7, 10, 11) The magnitude of the associations in these studies ranged between 1.15 to 1.29.(7, 10, 11) Among previous studies of infant paracetamol exposure and asthma development that adjusted for the child's experience of respiratory tract infections (6, 8, 16-19), three studies reported a positive association (6, 16, 19). These studies reported that paracetamol exposure during infancy was associated with a doubling in the risk of asthma development.(6, 16, 19) However, one of these studies indicated that the association was restricted to girls.(6) Our study is the first to evaluate the relative importance of prenatal versus infant paracetamol exposure able to account for common indications during both exposure periods. This allowed us to show that both prenatal and infant paracetamol exposure had independent positive associations with asthma development after adjustment for confounding by indication during both exposure periods.

Two previous studies examined prenatal ibuprofen exposure and asthma development. (8, 11) One of these studies examined both prenatal and infant ibuprofen exposure, reporting a positive association with infant ibuprofen exposure, adjusted odds ratio 1.20 (95 % confidence interval 1.02 to 1.40), but no strong evidence of an association with prenatal ibuprofen exposure, 1.17 (0.78-1.76).(8) Our results indicated a weak evidence for a positive association between prenatal ibuprofen exposure with asthma at 3 years and no strong evidence for an association with asthma at 7 years. We could not evaluate infant ibuprofen exposure as too few were exposed (0.1%).

Interpretation of main findings

Pregnant women who have asthma might be more likely to choose paracetamol as an analgesic/antipyretic compared to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs due to sensitization.(20) However, our results provided no strong evidence of an effect modification of maternal history of asthma on the observed associations.

This is the first study to address maternal conditions in pregnancy with and without the use of paracetamol in relation to asthma in the offspring. Maternal paracetamol use for respiratory tract infections/influenza, fever or pain all showed a positive association with asthma in the offspring, while maternal report of pain was the only indication that was positively associated with asthma in the offspring if the mother did not use paracetamol. Pain is highly subjective and likely influenced by a number of factors, and these findings therefore need to be replicated and explored in depth. One might speculate that maternal pain during pregnancy is a potential source of stress. A possible explanation for our finding is therefore the association between prenatal exposure to stress and asthma development.(21-24) However, our observed associations of prenatal and infant paracetamol exposure with asthma

development might also reflect the severity of the condition leading to paracetamol use. It was not possible to further evaluate this using the information available.

We cannot exclude the possibility that the association of prenatal and infant paracetamol exposure with asthma development might be partly mediated by later paracetamol exposure.

The evaluation of maternal paracetamol use outside of pregnancy and paternal paracetamol use was motivated by a negative controls approach.(12, 13) Evaluation of these negative controls allowed an assessment of the likelihood of unmeasured confounding by characteristics that might influence the propensity for using paracetamol. Only one study has previously evaluated maternal paracetamol use after pregnancy and paternal paracetamol use.(25) In line with the findings from this previous study, we found no strong evidence for an association between maternal paracetamol use outside of pregnancy or paternal paracetamol use with asthma in the offspring, supporting the conclusion that the results were not caused by underlying characteristics or health behavior.

If the observed association between paracetamol exposure and asthma development reflects a true effect, proposed biological mechanisms include the ability of paracetamol to induce oxidative stress, enhance Th2 cell polarization and mediation of non-eosinophilic inflammatory responses.(26, 27) Increased oxidative stress during pregnancy and infancy is hypothesized to increase the risk of asthma.(28) This hypothesis is also supported by studies reporting an inverse association between maternal antioxidant intake during pregnancy and asthma in the offspring.(29, 30) Results from the Avon Longitudinal Study of Parents and Children also indicate that maternal antioxidant gene polymorphism may modify the association between prenatal paracetamol exposure and asthma development.(7)

Ibuprofen is used for many of the same indications as paracetamol. According to Norwegian guidelines , ibuprofen is not recommended for pregnant women and infants who weigh less

than 10 kilograms.(9) Based on our results, we could not conclude with certainty that prenatal ibuprofen exposure did not have a similar positive association with asthma development as observed for prenatal paracetamol exposure, since we likely had limited power to detect an association with our outcomes at 7 years. Ibuprofen is a COX-1 inhibitor, contributing to an up-regulation of leukotrienes, thought to play a role in asthma pathogenesis.(31)

Strengths and limitations

Strengths of the current study include the size, detailed evaluation of different indications for prenatal paracetamol exposure, evaluation of prenatal ibuprofen exposure, in addition to the evaluation of maternal paracetamol use outside of pregnancy and paternal paracetamol use as negative controls. This is the first study comparing the association between prenatal exposure to different indications and use of paracetamol for different indications with development of asthma, and the first study examining the relative importance of prenatal versus infant paracetamol exposure in relation to asthma development that was able to adjust for confounding by indication during both exposure periods.

The main limitation of the information available in MoBa was the ability to account for the amount paracetamol used and severity of the underlying indications. However, by evaluating prenatal paracetamol exposure for more than one indication and during more than one time period of pregnancy, we evaluated two approaches to distinguish between amounts of exposure. The classification of prenatal and infant paracetamol exposure through questionnaires could have resulted in misclassification. Due to the prospective data collection, any misclassification of paracetamol exposure is unlikely to be differential by the child's asthma status. Another limitation is that the information available for the child's use of medications during the first 6 months of life did not include which specific condition the medications had been used for. By using maternal report of the child's asthma status there may also be misclassification of the outcome. However, maternal report that the child used

asthma medications in the past year on the 7 years questionnaire in MoBa compared well to dispensed asthma medications in the prescription registry.(32) A comparison of MoBa participants against all Norwegian women who gave birth during the inclusion period indicated that several high risk groups might be underrepresented.(15) This might influence the generalizability of our results.(33-35) Our study further required information from a number of follow-up questionnaires. A comparison of eligible individuals with and without the necessary follow-up information indicated that mothers of children with the necessary follow-up information were older, were more likely to have higher education and were less likely to smoke (Supplementary Table 1). We further evaluated bias due to loss to follow-up by using dispensed asthma medications as an additional outcome, which showed similar associations as the questionnaire based outcome.

Conclusion

Our study is by far the largest study to provide evidence that prenatal and infant paracetamol exposure have independent positive associations with asthma development. Our findings provided suggest that the associations could not be fully explained by confounding by indication. Paracetamol is the most commonly used analgesic/antipyretic among pregnant women and infants, and uncovering potential adverse effects is of public health importance. Based on the inherent challenges in observational studies, evidence from a randomized controlled trial would be beneficial.

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Contributors: The study was initiated by M.C.M and W.N., and designed by M.C.M., W.N., S.E.H., and P.N. M.C.M. performed the statistical analysis and wrote the initial draft with supervision from W.N., S.E.H. and P.N. Ø.K. and G.D.S. contributed with invaluable support for data analyses, interpretation of findings and critical revision of the manuscript. W.N. and M.C.M. obtained the financial support. All authors had full access to data, reviewed and approved the final version of the article submitted for publication. M.C.M. will act as the guarantor of the manuscript. The references have been checked for accuracy and completeness by M.C.M.The authors are grateful to all families participating in the Norwegian Mother and Child Cohort Study.

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Figure legends:

Figure 1 Illustration of sample selection

Table 1. Characteristics by prenatal and infant paracetamol exposure (N=53,169)

Characteristics	n	No exposure (%)	Prenatal exposure only (%)	Infant exposure only (%)	Both prenatal and infant exposure (%)
Maternal age, years					
<25	4,758	36.0	30.1	15.2	18.8
25-29	17,725	36.8	27.8	15.7	19.7
30-34	21,137	37.0	27.8	15.7	19.5
>=35	9,549	40.4	27.3	14.9	17.4
Maternal parity					
Primiparous	25,486	40.6	27.3	15.5	16.6
1	18,158	33.6	27.9	16.1	22.4
2	7,488	35.4	29.8	14.5	20.3
3 or more	2,037	38.9	28.8	14.3	17.9
Maternal education					
Less than high school	2,910	38.2	27.9	14.2	19.8
High school	14,175	37.6	29.9	14.1	18.4
Up to 4 years of college	22,841	36.1	27.7	15.9	20.3
More than 4 years of college	13,046	39.5	26.1	16.7	17.8
Missing	197	37.6	29.4	16.2	16.8
Maternal pre-pregnancy BMI					
Underweight (<18.5)	1,520	41.7	25.5	15.9	16.9
Normal weight (18.5-24.9)	34,625	39.2	26.8	16.0	18.0
Overweight (25-29.9)	11,247	33.8	30.1	14.9	21.2
Obese (>=30)	4,626	30.7	32.1	13.3	23.9
Missing	1,151	42.1	26.2	14.9	16.9
Maternal asthma					
No	49,338	38.2	27.6	15.5	18.7
Yes	3,831	28.5	31.9	15.2	24.4
Maternal RTI/influenza during pregnancy					
No	21,248	45.8	22.8	17.7	13.8
Yes	31,921	31.9	31.3	14.1	22.7
Maternal fever during pregnancy					
No	44,359	41.1	25.3	16.9	16.7
Yes	8,810	18.9	41.0	8.6	31.5
Maternal pain during pregnancy					
No	12,329	53.7	17.5	18.9	10.0
Yes	40,840	32.6	31.1	14.5	21.9
Maternal smoking during pregnancy					
No	48,947	37.8	27.6	15.6	19.0
Yes	3,970	32.6	31.8	14.1	21.4
Missing	252	38.5	31.8	11.1	18.7

Child gender					
Male	27,193	37.1	26.6	16.5	19.8
Female	25,976	37.8	29.3	14.5	18.4
Child birth weight, grams					
<2,500	1,332	38.5	28.8	12.8	19.9
2,500-2,999	4,505	39.6	26.3	16.0	18.1
3,000-3,499	15,523	38.3	27.6	15.6	18.5
3,500-4,000	20,023	37.1	27.9	15.7	19.3
>4000	11,764	36.0	28.8	15.2	20.0
Missing	22	31.8	27.3	13.6	27.3
Child breastfeeding the first 6 months					
None	1,360	34.6	29.8	13.4	22.2
Partial	28,191	35.3	28.5	15.6	20.7
Exclusive	23,618	40.2	27.1	15.6	17.1
Child RTI the first 6 months					
No	11,441	47.4	32.1	10.0	10.6
Yes	40,343	34.3	26.6	17.2	21.8
Missing	1,385	46.8	30.8	11.7	10.8
Child BMI at 6 months					
<16.1	12,573	38.4	28.0	15.1	18.6
16.1-17.0	12,559	37.2	28.1	15.5	19.2
17.1-18.0	12,743	37.1	28.4	15.4	19.1
>18.1	12,520	36.8	27.1	16.2	20.0
Missing	2,774	39.3	28.2	14.8	17.7
Prenatal and infant antibiotic exposure					
None	44,143	39.1	27.2	15.7	18.0
Prenatal only	6,387	28.8	33.7	12.9	24.6
Infant only	2,188	31.8	25.3	19.2	23.7
Prenatal and infant	451	23.7	31.0	14.2	31.0

BMI-body mass index; RTI - respiratory tract infections
The frequencies in this table are based on the study sample used to examine current asthma at 3 years.

RTI/influenza during pregnancy included maternal report of upper respiratory tract infections (ear, throat, sinus infections and/or colds) lower respiratory tract infections (pneumonia and/or bronchitis) and/or influenza.

Pain during pregnancy included maternal report of pelvic prolapse, back pain, neck/shoulder pain, migraine/head ache, fibromyalgia and/or unspecified muscle pain.

Table 2. The association of prenatal and infant paracetamol exposure with development of asthma

Current asthma at 3 years (N=53,169)				
Prenatal and infant paracetamol exposure	**N**	**% case**	**Unadjusted RR(95%CI)**	**Adjusted RR (95% CI)[a]**
No exposure	19,912	4.4	1	1
Prenatal exposure only	14,837	5.9	1.33 (1.21-1.46)	1.13 (1.02-1.25)
Infant exposure only	8,246	6.5	1.47 (1.32-1.63)	1.29 (1.16- 1.45)
Both prenatal and infant exposure	10,174	7.5	1.71 (1.55-1.88)	1.27 (1.14- 1.41)
Current asthma at 7 years (N=25,394)				
Prenatal and infant paracetamol exposure	**N**	**% case**	**Unadjusted RR(95%CI)**	**Adjusted RR (95% CI)[a]**
No exposure	9,905	3.9	1	1
Prenatal exposure only	7,240	5.6	1.44 (1.26-1.66)	1.27 (1.09- 1.47)
Infant exposure only	3,763	5.2	1.35 (1.14- 1.60)	1.24 (1.03 - 1.48)
Both prenatal and infant exposure	4,486	6.9	1.78 (1.54- 2.06)	1.49 (1.27- 1.75)
Dispensed asthma medications at 7 years (N=45,607)				
Prenatal and infant paracetamol exposure	**N**	**% case**	**Unadjusted RR(95%CI)**	**Adjusted RR (95% CI)[a]**
No exposure	17,840	3.9	1	1
Prenatal exposure only	12,974	5.2	1.33 (1.20- 1.48)	1.17 (1.04- 1.31)
Infant exposure only	6,708	5.2	1.33 (1.17- 1.51)	1.27 (1.11-1.46)
Both prenatal and infant exposure	8,085	5.8	1.50 (1.33- 1.68)	1.26 (1.10- 1.43)

[a] Associations adjusted for maternal age, parity, education, pre-pregnancy body-mass index, smoking during pregnancy, asthma, respiratory tract infections/influenza during pregnancy, fever during pregnancy, pain during pregnancy and antibiotic use during pregnancy, in addition to the child's gender, birth weight, breastfeeding the first 6 months of life, respiratory tract infections by 6 months, body mass index at 6 months and use of antibiotics by 6 months.

RTI/influenza during pregnancy included maternal report of upper respiratory tract infections (ear, throat, sinus infections and/or colds) lower respiratory tract infections (pneumonia and/or bronchitis) and/or influenza.

Pain during pregnancy included maternal report of pelvic prolapse, back pain, neck/shoulder pain, migraine/head ache, fibromyalgia and/or unspecified muscle pain.

Infant paracetamol exposure reflects the child's use of paracetamol the first 6 months of life.

The results presented are based on a complete case analysis. A total of 47,173 children were included in the multivariable analysis of current asthma at 36 months, 22,102 children in the analysis of current asthma at 7 years and 38,677 in the analysis of dispensed asthma medications at 7 years.

Table 3. The association of maternal indications and use of paracetamol during pregnancy with development of asthma in the offspring

Current asthma at 3 years (N=45,641)					
Exposure		**n**	**% cases**	**Unadjusted RR (95%CI)**	**Adjusted RR (95% CI)[a]**
Did not use paracetamol	Did not experience indications	4,660	3.4	1	1
	Experienced RTI/influenza only	3,623	3.8	1.12 (0.90- 1.41)	1.07 (0.85- 1.34)
	Experienced fever [b]	659	3.1	0.91 (0.58-1.44)	0.88 (0.56- 1.40)
	Experienced pain only	8,499	5.5	1.63 (1.36- 1.95)	1.47 (1.23- 1.76)
	Experienced more than one indication	10,717	5.9	1.74 (1.47- 2.07)	1.60 (1.35- 1.91)
Used paracetamol	For RTI/influenza only	1,817	5.7	1.70 (1.33- 2.17)	1.51 (1.18- 1.93)
	For fever [b]	3,234	6.5	1.91 (1.56- 2.35)	1.58 (1.28- 1.94)
	For pain only	9,575	6.9	2.06 (1.74- 2.45)	1.73 (1.46- 2.06)
	For more than one indication	2,857	7.8	2.32 (1.90- 2.84)	1.94 (1.58- 2.37)
Current asthma at 7 years (N=21,910)					
Exposure		**n**	**% cases**	**Unadjusted RR (95%CI)**	**Adjusted RR (95% CI)[a]**
Did not use paracetamol	Did not experience indications	2,377	3.5	1	1
	Experienced RTI/influenza only	1,810	4.3	1.23 (0.90- 1.68)	1.15 (0.83- 1.58)
	Experienced fever [b]	316	2.2	0.64 (0.30- 1.38)	0.65 (0.30- 1.38)
	Experienced pain only	4,075	4.5	1.29 (1.00- 1.67)	1.18 (0.90- 1.53)
	Experienced more than one indication	5,090	4.6	1.32 (1.03- 1.70)	1.23 (0.95- 1.58)
Used paracetamol	For RTI/influenza only	877	5.4	1.55 (1.09-2.21)	1.39 (0.97- 1.99)
	For fever [b]	1,418	5.5	1.58 (1.16- 2.15)	1.34 (0.98- 1.85)
	For pain only	4,623	6.2	1.81 (1.42- 2.30)	1.53 (1.19-1.96)
	For more than one indication	1,324	7.8	2.25 (1.69- 2.99)	1.91 (1.43- 2.55)
Dispensed asthma medications at 7 years (N=39,157)					
Exposure		**n**	**% cases**	**Unadjusted RR (95%CI)**	**Adjusted RR (95% CI)[a]**
Did not use paracetamol	Did not experience indications	4,107	3.5	1	1
	Experienced RTI/influenza only	3,067	3.0	0.87 (0.67- 1.13)	0.83 (0.64- 1.08)
	Experienced fever [b]	558	2.2	0.62 (0.34- 1.11)	0.63 (0.35- 1.14)
	Experienced pain only	7,548	4.5	1.28 (1.06- 1.55)	1.21 (0.99- 1.47)
	Experienced more than one indication	9,267	5.0	1.42 (1.18- 1.71)	1.36 (1.13-1.65)

Used paracetamol	For respiratory RTI /influenza only	1,452	4.6	1.33 (1.00- 1.76)	1.24 (0.93- 1.66)
	For fever [b]	2,509	5.6	1.60 (1.28- 2.01)	1.41 (1.12- 1.79)
	For pain only	8,263	5.9	1.71 (1.42- 2.05)	1.51 (1.25- 1.83)
	For more than one indication	2,386	6.4	1.83 (1.46- 2.29)	1.59 (1.26- 2.01)

RTI- respiratory tract infections

[a] Associations adjusted for maternal age, parity, education, pre-pregnancy body-mass index, smoking during pregnancy, asthma and antibiotic use during pregnancy

[b] The group who reported fever or use of paracetamol for fever were allowed to also report RTI/influenza or use of paracetamol for RTI/influenza. All other categories are mutually exclusive.

RTI/influenza during pregnancy included maternal report of upper respiratory tract infections (ear, throat, sinus infections and/or colds) lower respiratory tract infections (pneumonia and/or bronchitis) and/or influenza.

Pain during pregnancy included maternal report of pelvic prolapse, back pain, neck/shoulder pain, migraine/head ache, fibromyalgia and/or unspecified muscle pain.

This analysis excluded individuals who used paracetamol for other/unspecified reason. This included 7,528 children in the evaluated of current asthma at 3 years, 3,484 children in the evaluation of current asthma at 7 years and 6,450 children in the evaluation of dispensed asthma medications at 7 years.

The results presented are based on a complete case analysis. A total of 43,789 children were included in the multivariable analysis of current asthma at 36 months, 20,800 children in the analysis of current asthma at 7 years and 37,783 in the analysis of dispensed asthma medications at 7 years.

Table 4. The association of maternal use of ibuprofen and paracetamol during pregnancy with development of asthma in the offspring

Current asthma at 3 years (N=53,169)				
Ibuprofen and paracetamol use during pregnancy	**N**	**% case**	**Unadjusted RR (95%CI)**	**Adjusted RR (95% CI)[a]**
Neither	27,392	5.0	1	1
Only ibuprofen	766	7.0	1.41 (1.08- 1.84)	1.31 (1.00,1.72)
Only paracetamol	22,675	6.5	1.32 (1.23- 1.42)	1.11 (1.02, 1.19)
Both ibuprofen and paracetamol	2,336	6.6	1.34 (1.14- 1.58)	1.10 (0.93, 1.30)
Current asthma at 7 years (N=25,394)				
Ibuprofen and paracetamol use during pregnancy	**N**	**% case**	**Unadjusted RR (95%CI)**	**Adjusted RR (95% CI)[a]**
Neither	13,290	4.2	1	1
Only ibuprofen	378	4.9	1.16 (0.74- 1.83)	1.16 (0.73, 1.83)
Only paracetamol	10,608	6.1	1.44 (1.29- 1.61)	1.26 (1.12, 1.43)
Both ibuprofen and paracetamol	1,118	6.1	1.45 (1.14- 1.86)	1.28 (1.00, 1.65)
Dispensed asthma medications at 7 years (N=45,607)				
Ibuprofen and paracetamol use during pregnancy	**N**	**% case**	**Unadjusted RR (95%CI)**	**Adjusted RR (95% CI)[a]**
Neither	23,839	4.2	1	1
Only ibuprofen	709	4.8	1.13 (0.81- 1.58)	1.02 (0.73, 1.44)
Only paracetamol	19,139	5.5	1.29 (1.19- 1.40)	1.12 (1.03, 1.23)
Both ibuprofen and paracetamol	1,920	5.3	1.24 (1.02- 1.52)	1.03 (0.83, 1.26)

[a] Associations adjusted for maternal age, parity, education, pre-pregnancy body-mass index, smoking during pregnancy, asthma, respiratory tract infections/influenza during pregnancy, pain during pregnancy, fever during pregnancy and antibiotic use during pregnancy

The results presented are based on a complete case analysis. A total of 51,011 children were included in the multivariable analysis of current asthma at 36 months, 24,114 children in the analysis of current asthma at 7 years and 44,009 in the analysis of dispensed asthma medications at 7 years.

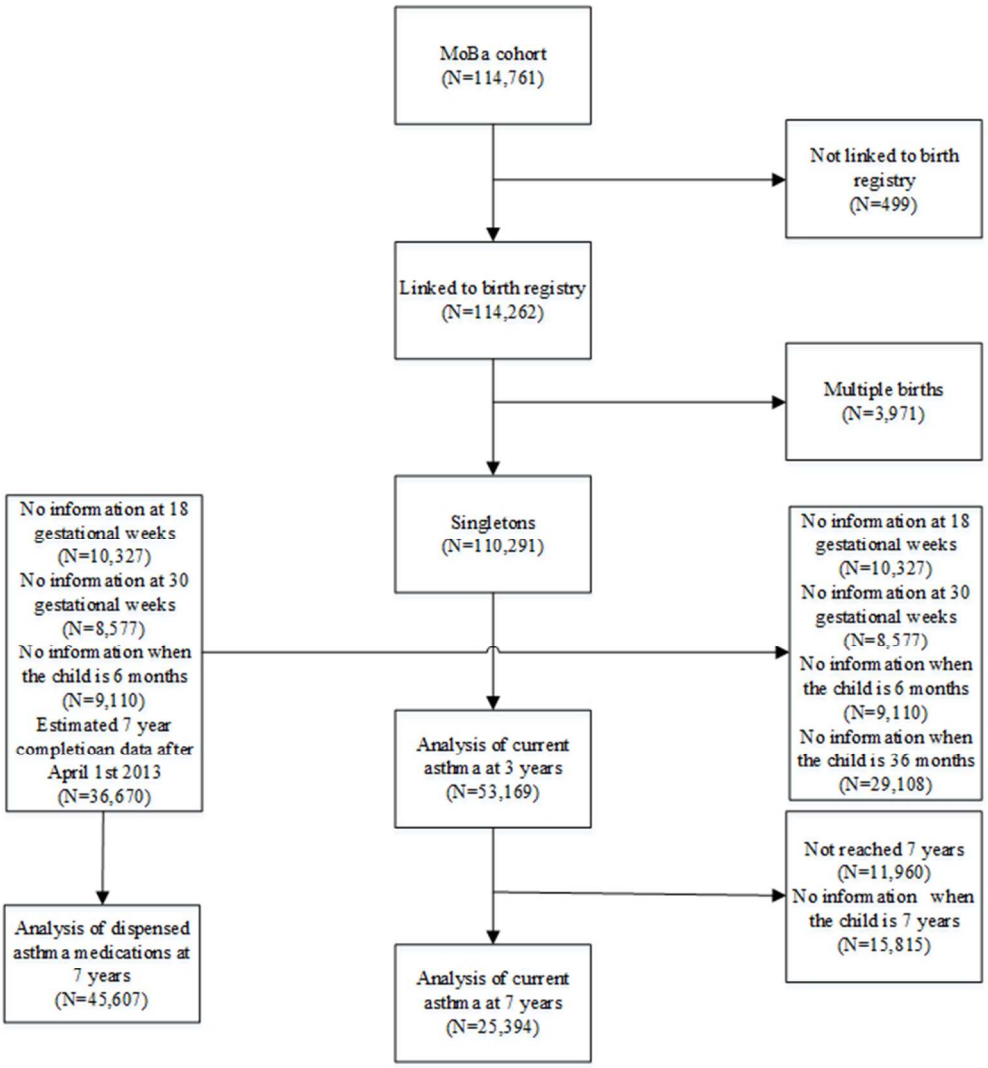

Figure 1 Illustration of sample selection