The role of combined prenatal and postnatal paracetamol exposure on asthma development: the Czech ELSPAC study

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What is already known?

- Paracetamol is analgesic and antipyretic of first choice for today´s pregnant women and small babies.
- Published studies showed that prenatal paracetamol exposure was associated with asthma development.
- Postnatal exposure to paracetamol was also found to be associated with higher risk of asthma development although combination of pre- and postnatal exposure to paracetamol was only rarely investigated.

What this study adds?

- Additive effect of combination of prenatal and postnatal paracetamol exposure leads to higher risk of asthma development in specific population using more aspirin than paracetamol-based drugs.
- The increase in risk of asthma development for those exposed to aspirin is smaller than for those exposed to paracetamol.
- Paracetamol still should remain the analgesic and antipyretic of first choice for pregnant women and small babies but mothers should be better informed to consider every paracetamol use carefully.

Abstract

Background:

Prenatal and postnatal paracetamol exposure has been previously associated with asthma development in childhood in Western populations. We explore the association between prenatal and postnatal paracetamol exposure and asthma development in Central European sample of Czech children, suggesting possible additive effect of the both exposures. Furthermore, since aspirin had been used more widely during study data collection in Central Europe, we also compared asthma development for those exposed to paracetamol and aspirin.

Methods:

We used data from 3329 children born in 1990s as members of the prospective Czech European longitudinal study of pregnancy and childhood (ELSPAC). Data about prenatal and postnatal paracetamol and aspirin exposure, and potential covariates were obtained from questionnaires completed by mothers. Data about incident asthma were obtained from paediatrician health records.

Results:

60.9% of children received paracetamol only postnatally, 1.5% only prenatally and 4.9% of children were exposed both during pregnancy and infancy. Prevalence of asthma in following population was 5% at 11 years. Being exposed to paracetamol both in pre- and post-natal period was associated with asthma development (unadjusted OR 1.98, 95% CI 1.02-3.87). Being exposed only in postnatal period was also significantly associated with increased risk of asthma. No association between prenatal exposure only and outcome was found. A higher but non-significant risk of asthma was observed for those whose mothers used paracetamol during pregnancy in comparison with those who used aspirin.

Conclusions:

The main findings of this prospective birth cohort study add to previous observations linking prenatal and early postnatal paracetamol exposure to asthma development. However, the

magnitude of effect is relatively modest and therefore we recommend paracetamol to remain the analgesic and antipyretic of choice throughout pregnancy and early childhood.

Introduction

Asthma is one of the most common non-communicable diseases.[1] Asthma-like symptoms affect the quality of life, psychological functioning and the well-being of children and their families.[2] Asthma pathogenesis is attributed to both genetic and environmental factors.[3] Environmental risk factors of asthma development include increasing pollution levels,[4] dietary change[5] and hygiene effects,[6] although the evidence to support these remains controversial.[7-9] It has also been suggested that asthma might be linked to paracetamol exposure
in pregnancy and early life.[10]

Paracetamol is a widely used non-steroidal analgesic and antipyretic drug.[11] In the 1990s, when aspirin was found to be associated with Reyes syndrome,[12] it replaced aspirin as the analgesic and antipyretic of first choice for pregnant women. Aspirin, also known as acetylsalicylic acid (ASA), has been known to be an effective analgesic and antipyretic drug. Aspirin is nonsteroidal anti-inflammatory drug which inhibit the activity of cyclooxygenase thereby the synthesis of prostaglandins and thromboxanes.[13] Currently, aspirin is not recommended for pregnant mother and children less than 16 years of age because it causes severe side effects such as the Reye syndrome.[14, 15] Nowadays paracetamol is the recommended drug for self-medication to relieve higher temperature, pain and other discomforts in pregnant women and in young children. Paracetamol has only weak anti-inflammatory properties. The action of paracetamol at a molecular level is unclear but it is known that paracetamol induced hypothermia is also accompanied by a reduction in brain prostaglandin concentrations and analgesic effect is linked with modulating of serotonergic system.[16]

Previous studies demonstrated an association between prenatal exposure to paracetamol and asthma development.[17-19] Postnatal exposure to paracetamol has been also found to be associated with higher risk of asthma development.[20-22] Only one Norwegian study demonstrated an association between a combination of prenatal and postnatal exposures and asthma development, suggesting possible additive effect of both exposures.[23] The habits of self-medication in pregnancy were different in Central Europe in the 1990s, and while almost half of the mothers in above mentioned Norwegian study used paracetamol in prenatal period, as our

Czech ELSPAC study data suggests, only slightly more than 10% did the same in the Czech Republic and aspirin was still used more frequently. So far, there have been no studies from Central or Eastern Europe evaluating the association between prenatal and postnatal paracetamol exposures and asthma development in childhood.

We evaluated the association of prenatal and infant paracetamol exposure with asthma development in Czech children before age 11. To enrich our analysis, we additionally explored the association between maternal cold/influenza experience during pregnancy and development of asthma in comparison to the association between asthma development and paracetamol use while experiencing cold/influenza. Furthermore, since aspirin had been used more widely in pregnancy during study period, we also compared asthma development for those exposed to paracetamol and aspirin.

Methods

Study population

Study data were derived from the Czech part of the European Longitudinal Study of Pregnancy and Childhood (ELSPAC), a prospective birth cohort study carried out in the Czech Republic. The ELSPAC study investigated environmental and other factors affecting the health and development of children from the prenatal period until adulthood. Mothers from the Brno and Znojmo regions of Czechoslovakia (now the Czech Republic) who were expected to deliver baby between 1 March 1991 and 30 June 1992 were selected as the target study population. The participation rate of invited pregnant women was 96 %. Pairs of mothers and children were followed mainly by means of health records from maternity hospitals/paediatricians and self-reported questionnaires completed by parents and later on by the children themselves. A total of 4,811 mothers completed the first self-reported questionnaire in the 20^{th} week of pregnancy. Current analysis is based on 3,329 children with information about prenatal and postnatal paracetamol exposure and health records from paediatricians (children with complete data until the age of 11). Informed consent was obtained from all study participants during each wave of

data collection. Ethics approval for all aspects of data collection was obtained from local ethics committees. Additional details about the study have been published earlier.[24]

Exposure

Information about paracetamol and aspirin use was obtained from the self-reported questionnaires. Mothers were asked at pregnancy (week 20) how often they had taken paracetamol/aspirin ("not at all", "sometimes", "most days", and "every day") during pregnancy. Paracetamol was taken frequently ("most days", and "every day") by less than 1% of women. Therefore we combined these categories into a binary variable (exposed to paracetamol yes/no). Subsequently, at ages 6 and 18 months of the children, mothers were asked if they had given their infants paracetamol either from birth or from the age of 6 months. To distinguish between prenatal and postnatal paracetamol exposure, we used the following mutually exclusive exposure categories: "no exposure", "prenatal exposure only", "postnatal exposure only" and "both exposures". Prenatal and postnatal exposure was defined according to Magnus et al.[23] The similar procedure was used to assess prenatal aspirin exposure.

Outcomes

On the basis of paediatric health records from age 3, 5, 7 and 11 years, we defined a group of those children who had at least one record of paediatrician-diagnosed asthma (coded as J45 or J46 in ICD-10, or 493.0, 493.1 or 493.9 in ICD-9) treated by medications. Please see Supplementary Table 1.

Covariates used in the analysis

Information on potential covariates (potential confounders and mediators) was collected mainly from self-reported questionnaires completed by mothers and fathers during pregnancy, infancy and childhood. Potential parental covariates included age, education, marital status, parity, asthma history, maternal pre-pregnancy BMI and maternal influenza experience during pregnancy. Potential child characteristics included sex, birth weight and breastfeeding in the first 6 months. Environmental characteristics included dwelling type, pet presence at home, maternal smoking, passive smoking maternal alcohol consumption and visits kindergarten at 3 years. The distribution of covariates included in regression models is shown in Table 1.

Statistical analyses

All statistical analyses were carried out using STATA software (version 14). Firstly, we performed unadjusted logistic regression to investigate the association between prenatal and early life paracetamol exposure and asthma development in childhood. We subsequently constructed an adjusted logistic regression model including all potential risk factors (Table 2).

Secondly, a similar model was constructed to evaluate whether cold/influenza experience during pregnancy affect the role of paracetamol use in asthma development confounding asthma development. We constructed four mutually exclusive categories for possible interaction between paracetamol use and cold/influenza: we divided respondents to those whose mothers used paracetamol but did not experience cold/influenza, those whose mothers did not use paracetamol but experienced cold/influenza, those who did not use paracetamol and did not experience cold/influenza and those who did use paracetamol and experienced cold/influenza. We then examined the association between asthma development and these four combinations by unadjusted and adjusted logistic regression (Table 3).

Thirdly, since paracetamol and aspirin are used for similar indications, we examined the association between mutually exclusive categories, i.e. “no exposure”, “only paracetamol exposure”, “only aspirin exposure” and “both paracetamol and aspirin exposure” during pregnancy and asthma development (Table 4).

Results

Information about prenatal and postnatal exposure to paracetamol (postnatal exposure up to 18 months) and completed health record about asthma diagnosis were available for a total of 3,329 children who were thus included in this analysis. 40 % of pregnant mothers were aged 20 to 25 years, 88 % were married and about 3% have had asthma. A comprehensive overview of study subject characteristics is provided in Table 1.

The frequency of combined prenatal and postnatal paracetamol exposure is shown in Table 2. A total of 32.7 % of children were never exposed to paracetamol, neither during pregnancy or up to

the age of 18 months, 1.5 % was exposed only during pregnancy, 60.9 % were exposed only postnatally and 4.9 % were exposed both during pregnancy and infancy (up to 18 months).

By the age of 11, 5 % of all children had a record of physician-diagnosed asthma. The lowest asthma prevalence (3.7 %) was reported for the non-exposed group while the highest asthma prevalence (7.0 %) was found in the group with both pre- and postnatal exposure.

Table 2 also shows unadjusted and adjusted odds ratios (OR) of the association between paracetamol exposure and asthma development. Pre- and post-natal exposure to paracetamol was associated with asthma development (unadjusted OR 1.98, 95 % CI 1.02–3.87). Postnatal paracetamol exposure was slightly associated with asthma (unadjusted OR 1.54, 95 % CI 1.06–2.23). No statistically significant relationship was identified in the case of prenatal paracetamol exposure.

In the multivariable model the association between prenatal and postnatal paracetamol exposure and asthma development remained practically unchanged. Factors contributing to asthma included asthma family history, maternal education and pet presence at home during the first 6 months. In addition, the male gender was also found to contribute to the higher risk of asthma development.

In a further analysis we compared the risk of prenatal cold/influenza experience and prenatal paracetamol exposure for asthma development. The results indicated that the risk of childhood asthma among mothers who suffered from cold/influenza and used paracetamol was 30 % higher than in the case of the non-paracetamol exposed group of mothers. On the other hand, children of mothers who did not experience cold/influenza but used paracetamol for different indications were at a 42 % higher risk of asthma. All of these results are statistically non-significant. No significant changes in odds ratios and confidential intervals occurred following adjustment (Table 3).

Prenatal aspirin exposure was reported for 16.0 % of mothers. Prenatal paracetamol exposure was reported for 6.5 % of mothers. A higher risk of asthma was observed for those who used paracetamol during pregnancy in comparison with those who used aspirin or nothing. However, these associations were not statistically significant (Table 4).

Discussion

In this analysis we observed a modest association between prenatal and postnatal exposure to paracetamol and asthma development during childhood. Our results also demonstrated a higher risk of asthma among children exposed only in early childhood. No association between exposure and outcome was found among children who were only exposed prenatally.

Similar trends were observed in a Norwegian study which analysed prenatal and postnatal paracetamol exposure using a similar pattern. In the analysis by Magnus et al[23] relative risks of the association between asthma and paracetamol were 1.17 for prenatal exposure only, 1.27 for postnatal exposure only and 1.26 for both exposures. Moreover, another earlier study examining the association between cumulative (prenatal and postnatal) exposure to paracetamol and asthma development, reported a positive association with adjusted OR 1.32 and 95 % CI 1.06–1.65.[18] Our findings are also largely in accordance with results summarized in a previous meta-analysis focusing on the association between asthma and paracetamol exposure in different periods of child development.[25, 26] These two meta-analyses reported odds ratios 1.15 and 1.28 for prenatal exposure, and 1.39 and 1.47 for postnatal exposure.

Following adjustment for potential risk factors, a higher risk of asthma was identified among children with a parental asthma history. Genetic risk factors were reported previously in studies associating prenatal paracetamol exposure and childhood asthma development.[27] Furthermore, gender was found to be a clinically relevant robust confounder. Our findings support previous results showing the incidence and prevalence of asthma have been found to be higher among boys than among girls up to the age of 14.[28, 29] Previous findings, however, are not entirely consistent, with a smaller prospective study focusing on potential environmental factors showing opposite results.[30]

The induction of asthma by paracetamol is biologically plausible. Paracetamol freely crosses the placenta. The potential mechanism of the toxic effect of paracetamol might manifest itself by depleting antioxidant capacity,[31] thereby increasing the generation of reactive oxygen species that could contribute to asthma-related airway inflammation.[32] On the other hand, childhood asthma is associated with perinatal cold/influenza, which is the most frequent indication for use of paracetamol[33] and prenatal cold/influenza is also a risk factor for childhood asthma

development. Therefore, we decided to assess the role of these two potentially distinct influences: maternal paracetamol exposure and cold/influenza experience. Our results demonstrated that prenatal paracetamol exposure is a higher risk for asthma development than exposure to cold/influenza only. However, though our results were not statistically significant, they were in accordance with the results of a previous study which demonstrated statistically significant results.[23]

Our comparison of the risk posed by paracetamol and aspirin for asthma development was historically motivated. In the 1990s, these two medications were used by pregnant Czech women in a ratio of 1:2 (Table 3). This fact enabled us to evaluate whether associations with prenatal paracetamol use were specific for this particular analgesic or whether they were associated with prenatal analgesic use generally. Our results indicate weak and statistically non-significant differences between individual groups.

More recent studies demonstrated similar patterns for prenatal analgesic and antipyretic exposure. Two studies recently assessed the association between prenatal exposure to ibuprofen and asthma development and found some elevation of risk of asthma associated with ibuprofen exposure.[18, 23] Rebordosa demonstrated that children prenatally exposed to aspirin and ibuprofen had no increased risk of asthma development in childhood.[17] Nevertheless, results from ALSPAC showed that frequent aspirin use in pregnancy was associated with an increased risk of wheezing, i.e. the most common preliminary symptom of asthma, only up to 6 months of age.[34]

Strengths and limitations

At the beginning of the Czech ELSPAC study the population from which our cohort was drawn was broadly representative of the entire Czech Republic.[24] Although we included only approximately 70% of original study sample in our analysis, the prevalence of asthma reported in ELSPAC was found to be in accordance with the prevalence of asthma in Czech children in the 1990s [35] but these data are lower than data presented by ISAAC for Northern and Eastern Europe (prevalence of asthma in 6-7 years old male 9.9 and female 7.5).[36] From the paracetamol exposure point of view we excluded 35 % of the study population due to a lack of information about prenatal or postnatal paracetamol exposure. Therefore, we cannot rule out the possibility that the exclusion of children without complete information might bias our findings.

However, for the adverse effects of paracetamol exposure on asthma development to be misleading, there would have to be a protective effect of equal magnitude in those children who were not included, which seems unlikely, especially because we have replicated the previous findings of another cohort.[23]

Study limitations included low number of children in some exposure categories and thus related low analytical power particularly for comparisons with those exposed to paracetamol only in pregnancy, and also a lack of detailed information about the indication of prenatal and early infancy paracetamol exposure. The lack of more detailed information regarding the frequency of paracetamol exposure in both examined periods likewise posed a potential limitation. Due to a lack of positive responses, data on the frequency of prenatal paracetamol exposure were reduced to a binary variable (used/did not use paracetamol). Nevertheless, this reclassification is likely random with respect to asthma development because only few mothers took paracetamol during pregnancy on a daily basis. Due to the prospective nature of the data collection, any misclassification of paracetamol exposure is unlikely to be altered by a child's asthma status. Furthermore, birth weight could act as potential mediators between prenatal exposure to paracetamol and study outcome (and thus the multivariable models should not be adjusted for this variable). While we decided to keep birthweight in the final presented model, the results from model excluding birth weight were virtually identical to presented ones.

The main findings of this prospective birth cohort study add to previous findings linking prenatal and early postnatal paracetamol exposure to asthma development. The association, however, was not found to be strong and the causal relationship could not be confirmed by this study. Thus, we recommend that paracetamol remains the analgesic and antipyretic of choice throughout pregnancy and early childhood, but it should be used at the lowest possible dosage and at the shortest possible time because of association between prenatal paracetamol exposure and many health problems.[37] Similarly, postnatal paracetamol use should be also considered carefully.

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Competing Interests

None declared.

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Contributorship statement

All authors contributed to preparation and writing of the manuscript. All authors reviewed and approved the final version of this manuscript. LK contributed to the design of the study and lead the data collection. PP and JS prepared data for the analyses. PP analysed data. HP advised on the analyses. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References:

1. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2009;64(6):476-83.
2. Marsac ML, Funk JB, Nelson L. Coping styles, psychological functioning and quality of life in children with asthma. Child Care Health Dev. 2007;33(4):360-7.
3. Nystad W, Roysamb E, Magnus P, Tambs K, Harris JR. A comparison of genetic and environmental variance structures for asthma, hay fever and eczema with symptoms of the same diseases: a study of Norwegian twins. International Journal of Epidemiology. 2005;34(6):1302-9.
4. Brauer M, Hoek G, Van Vliet P, Meliefste K, Fischer PH, Wijga A, et al. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. Am J Respir Crit Care Med. 2002;166(8):1092-8.
5. Ellwood P, Asher MI, Bjorksten B, Burr M, Pearce N, Robertson CF. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. ISAAC Phase One Study Group. Eur Respir J. 2001;17(3):436-43.
6. Platts-Mills TA. Asthma severity and prevalence: an ongoing interaction between exposure, hygiene, and lifestyle. PLoS Med. 2005;2(2):e34.
7. Anderson HR, Butland BK, van Donkelaar A, Brauer M, Strachan DP, Clayton T, et al. Satellite-based estimates of ambient air pollution and global variations in childhood asthma prevalence. Environ Health Perspect. 2012;120(9):1333-9.
8. Standl M, Sausenthaler S, Lattka E, Koletzko S, Bauer CP, Wichmann HE, et al. FADS gene variants modulate the effect of dietary fatty acid intake on allergic diseases in children. Clin Exp Allergy. 2011;41(12):1757-66.
9. Brooks C, Pearce N, Douwes J. The hygiene hypothesis in allergy and asthma: an update. Curr Opin Allergy Clin Immunol. 2013;13(1):70-7.
10. Beasley R, Clayton T, Crane J, von Mutius E, Lai CK, Montefort S, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. Lancet. 2008;372(9643):1039-48.
11. Barr RG. Does paracetamol cause asthma in children? Time to remove the guesswork. Lancet. 2008;372(9643):1011-2.
12. McGovern MC, Glasgow JF, Stewart MC. Lesson of the week: Reye's syndrome and aspirin: lest we forget. Bmj. 2001;322(7302):1591-2.
13. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971;231(25):232-5.
14. Sachdeva P, Patel BG, Patel BK. Drug Use in Pregnancy; a Point to Ponder! Indian J Pharm Sci. 71. India2009. p. 1-7.
15. Macdonald S. Aspirin use to be banned in under 16 year olds. Bmj. 3252002. p. 988.
16. Graham GG, Scott KF. Mechanism of action of paracetamol. Am J Ther. 2005;12(1):46-55.
17. Rebordosa C, Kogevinas M, Sorensen HT, Olsen J. Pre-natal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study. Int J Epidemiol. 2008;37(3):583-90.
18. Sordillo JE, Scirica CV, Rifas-Shiman SL, Gillman MW, Bunyavanich S, Camargo CA, Jr., et al. Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children. J Allergy Clin Immunol. 2015;135(2):441-8.
19. Shaheen SO, Newson RB, Smith GD, Henderson AJ. Prenatal paracetamol exposure and asthma: further evidence against confounding. Int J Epidemiol. 2010;39(3):790-4.

20. Kreiner-Moller E, Sevelsted A, Vissing NH, Schoos AM, Bisgaard H. Infant acetaminophen use associates with early asthmatic symptoms independently of respiratory tract infections: the Copenhagen Prospective Study on Asthma in Childhood 2000 (COPSAC(2000)) cohort. J Allergy Clin Immunol. 2012;130(6):1434-6.
21. Wickens K, Beasley R, Town I, Epton M, Pattemore P, Ingham T, et al. The effects of early and late paracetamol exposure on asthma and atopy: a birth cohort. Clin Exp Allergy. 2011;41(3):399-406.
22. Cohet C, Cheng S, MacDonald C, Baker M, Foliaki S, Huntington N, et al. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. Journal of Epidemiology and Community Health. 2004;58(10):852-7.
23. Magnus MC, Karlstad O, Haberg SE, Nafstad P, Davey Smith G, Nystad W. Prenatal and infant paracetamol exposure and development of asthma: the Norwegian Mother and Child Cohort Study. Int J Epidemiol. 2016;45(2):512-22.
24. Piler P, Kandrnal V, Kukla L, Andryskova L, Svancara J, Jarkovsky J, et al. Cohort Profile: The European Longitudinal Study of Pregnancy and Childhood (ELSPAC) in the Czech Republic. Int J Epidemiol. 2016.
25. Cheelo M, Lodge CJ, Dharmage SC, Simpson JA, Matheson M, Heinrich J, et al. Paracetamol exposure in pregnancy and early childhood and development of childhood asthma: a systematic review and meta-analysis. Arch Dis Child. 2015;100(1):81-9.
26. Etminan M, Sadatsafavi M, Jafari S, Doyle-Waters M, Aminzadeh K, Fitzgerald JM. Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. Chest. 2009;136(5):1316-23.
27. Shaheen SO, Newson RB, Henderson AJ, Headley JE, Stratton FD, Jones RW, et al. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. Clin Exp Allergy. 2005;35(1):18-25.
28. Zein JG, Erzurum SC. Asthma is Different in Women. Current Allergy and Asthma Reports. 2015;15(6):10.
29. de Marco R, Locatelli F, Sunyer J, Burney P, European Community Resp Hlth S. Differences in incidence of reported asthma related to age in men and women - A retrospective analysis of the data of the European Respiratory Health Survey. American Journal of Respiratory and Critical Care Medicine. 2000;162(1):68-74.
30. Bakkeheim E, Mowinckel P, Carlsen KH, Haland G, Carlsen KC. Paracetamol in early infancy: the risk of childhood allergy and asthma. Acta Paediatr. 2011;100(1):90-6.
31. Nuttall SL, Khan JN, Thorpe GH, Langford N, Kendall MJ. The impact of therapeutic doses of paracetamol on serum total antioxidant capacity. J Clin Pharm Ther. 2003;28(4):289-94.
32. Dworski R. Oxidant stress in asthma. Thorax. 2000;55 Suppl 2:S51-3.
33. Illi S, Weber J, Zutavern A, Genuneit J, Schierl R, Strunz-Lehner C, et al. Perinatal influences on the development of asthma and atopy in childhood. Ann Allergy Asthma Immunol. 2014;112(2):132-9.e1.
34. Shaheen SO, Newson RB, Sherriff A, Henderson AJ, Heron JE, Burney PG, et al. Paracetamol use in pregnancy and wheezing in early childhood. Thorax. 2002;57(11):958-63.
35. Kratenova J, Puklova V. Prevalence of asthma and allergies in children in the Czech republic Prague: National Institute of Public Health; 2008 [Available from: http://www.szu.cz/tema/zivotni-prostredi/vyskyt-astmatu-a-alergii-u-deti.
36. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global synthesis. Allergol Immunopathol (Madr). 2013;41(2):73-85.
37. Toda K. Is acetaminophen safe in pregnancy? Scand J Pain. 2017.

Table 1: Characteristics of the population and potential covariates evaluated and finally included in the analysis (N=3,329)

Characteristics	%	n	No exposure (%)	Prenatal exposure only (%)	Postnatal exposure only (%)	Both prenatal and postnatal exposure (%)
Maternal age, years						
< 19	11.1	370	41.6	0.8	52.2	5.4
20-24	38.9	1294	35.1	1.2	59.4	4.3
25-30	33.5	1115	25.0	1.5	68.2	5.3
> 31	16.5	550	30.9	2.2	60.2	6.7
Maternal education						
Primary	34.9	1160	39.2	1.6	55.3	3.9
Secondary	44.6	1483	29.3	1.4	64.0	5.4
University	19.4	646	24.6	1.2	67.5	6.7
Missing	1.2	40	22.5	2.5	67.5	7.5
Marital status						
Married	87.8	2923	31.6	1.2	62.3	4.9
Divorced/widowed	2.7	91	27.5	3.3	60.4	8.8
Single	7.9	264	35.6	2.7	54.6	7.2
Missing	1.5	51	29.4	3.9	62.8	3.9
Parity						
0	48.7	1621	36.8	1.1	57.9	4.3
1	38.8	1293	25.1	1.5	67.6	5.9
2	7.7	255	31.0	2.8	59.6	6.7
3+	2.5	84	31.0	4.8	57.1	7.1
Missing	2.3	76	42.1	1.3	54.0	2.6
Paternal age, years						
< 25	28.0	932	37.0	1.1	57.9	4.0
25-30	33.2	1104	28.4	1.5	65.1	4.9
30-35	17.5	584	27.1	0.7	67.3	5.0
> 35	12.0	398	33.9	3.0	56.3	6.8
Missing	9.3	311	33.8	1.6	56.9	7.7
Mother have had asthma						
Yes	2.85	95	36.8	2.1	47.4	13.7
No	92.16	3068	31.4	1.4	62.3	4.9
Missing	4.99	166	36.1	1.8	57.8	4.2
Father have had asthma						
Yes	4.1	2878	31.8	1.4	61.7	5.1
No	86.5	136	22.8	3.7	70.6	2.9
Missing	9.5	315	35.2	1.3	57.1	6.4
Pre-pregnancy maternal BMI						
< 18.5	8.1	270	29.6	1.5	62.6	6.3
18.5–24.9	73.9	2459	31.0	1.3	62.5	5.2
25–29.9	10.4	347	32.9	1.4	61.4	4.3
> 30	2.8	92	34.8	2.2	56.5	6.5
Missing	4.8	161	42.9	2.5	51.6	3.1

Cold/influenza during pregnancy						
No	68.7	2286	31.8	1.3	63.1	3.9
Yes, (0–3 months)	17.9	596	29.5	2.0	60.1	8.4
Yes, (4–9 months)	6.3	211	33.2	2.8	53.6	10.4
Missing	7.1	236	36.0	0.4	59.3	4.2
Prenatal exposure to aspirin						
No	83.9	2,793	32.6	1.0	62.4	4.0
Yes	15.7	523	27.9	3.6	57.7	10.7
Missing	0.4	13	7.7	7.7	53.9	30.8
Child gender						
Male	52.3	1740	30.4	1.3	63.6	4.7
Female	47.7	1589	33.1	1.6	59.9	5.5
Birth weight (g)						
< 2,500	5.3	175	40.6	1.7	50.3	7.4
2,500–3,900	83.9	2792	31.2	1.5	62.2	5.1
> 3,900	8.9	297	30.3	1.0	64.7	4.0
Missing	2.0	65	36.9	1.5	55.4	6.2
Exclusive breastfeeding of child						
None	17.6	586	32.6	1.9	60.6	5.0
< 6 months	66.5	2214	32.2	1.3	61.0	5.5
> 6 months	12.8	425	28.0	1.2	67.1	3.8
Missing	3.1	104	32.7	2.9	59.6	4.8
Dwelling type						
House	28.9	963	33.5	1.6	60.8	4.2
Flat	68.1	2266	31.2	1.5	61.8	5.6
Missing	3.0	100	27.0	0.0	68.0	5.0
Pet at home						
Yes	31.6	1053	34.6	1.6	58.2	5.6
No	66.5	2213	30.5	1.4	63.3	4.8
Missing	1.9	63	28.6	0.0	61.9	9.5
Visits kindergarten at 3 years						
Yes	28.1	934	26.9	1.7	65.9	5.6
No	50.9	1695	29.1	0.9	64.7	5.4
Missing	21.0	700	44.7	2.4	48.9	4.0
Smoking during pregnancy						
Non-smoker	58.9	1960	32.4	1.1	62.1	4.4
Stop-smoker	33.1	1101	30.3	1.6	61.9	6.1
Smoker	6.9	228	34.2	3.5	55.7	6.6
Missing	1.2	40	27.5	0.0	67.5	5.0
Passive smoking at 3 years						
Yes	69.8	2325	27.3	1.2	65.8	5.7
No	9.4	314	35.4	1.6	59.6	3.5
Missing	20.7	690	45.1	2.2	48.7	4.1
Alcohol use in first trimester of pregnancy						
Never	67.1	2232	32.3	1.3	62.0	4.4
< 1x week	27.2	905	30.9	1.6	61.0	6.5
> 1x week	4.4	146	28.1	2.7	60.3	8.9
Missing	1.4	46	32.6	0.0	63.0	4.4

Frequencies in this table are based on the study sample.

Table 2: The association between prenatal and postnatal paracetamol exposure and asthma development (diagnosed up to age 11 by paediatricians)

Asthma	**% case**	**n**	**Unadjusted OR (95 % CI)**	**Adjusted OR (95 % CI)**
No exposure to paracetamol	3.7	1057	1	1
Only prenatal exposure to paracetamol	4.2	48	1.14 (0.27 - 4.87)	1.12 (0.25 - 4.98)
Only postnatal exposure to paracetamol	5.6	2053	1.54 (1.06 - 2.23)	1.56 (1.06 - 2.30)
Both exposures to paracetamol	7.0	171	1.98 (1.02 - 3.87)	1.83 (0.91 - 3.71)

Adjusted for mother age, mother education, marital status, parity, father age, mother asthma history, father asthma history, pre-pregnancy BMI, cold/influenza during pregnancy, child gender, birth weight, breastfeeding period, type of house, pet at house, visit kindergarten at the age of 3, mother smoking during pregnancy, passive smoking at age of 3, mother alcohol consumption during first trimester.

Table 3: The association of maternal cold/influenza and use of paracetamol during pregnancy with asthma development in childhood

Asthma	% case	n	Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
mother did not experience influenza / did not use paracetamol	4.9	2697	1	1
mother did not experienced influenza /use paracetamol	6.8	148	1.42 (0.73 - 2.76)	1.45 (0.72 - 2.91)
mother experienced influenza / did not use paracetamol	4.9	874	1.01 (0.71 - 1.44)	1.01 (0.71 - 1.46)
mother experienced influenza / use paracetamol	6.3	111	1.32 (0.60 - 2.89)	1.38 (0.61 - 3.14)

Adjusted for mother age, mother education, marital status, parity, father age, mother asthma history, father asthma history, pre-pregnancy BMI, cold/influenza during pregnancy, child gender, birth weight, breastfeeding period, type of house, pet at house, visit kindergarten in the age of 3, mother smoking during pregnancy, passive smoking at age of 3, mother alcohol consumption during first trimester.

Table 4: The association of paracetamol/aspirin exposure in pregnancy with asthma development in childhood

Asthma	**% case**	**n**	**Unadjusted OR (95 % CI)**	**Adjusted OR (95 % CI)**
Neither	4.6	3324	1	1
Only paracetamol	6.5	170	1.43 (0.76 - 2.70)	1.50 (0.77 - 2.90)
Only aspirin	6.0	532	1.33 (0.90 - 1.96)	1.36 (0.90 - 2.05)
Both	6.2	97	1.37 (0.59 - 3.17)	1.23 (0.50 - 2.98)

Adjusted for mother age, mother education, marital status, parity, father age, mother asthma history, father asthma history, pre-pregnancy BMI, influenza during pregnancy, child gender, birth weight, breastfeeding period, type of house, pet at house, visit kindergarten at the age of 3, mother smoking during pregnancy, passive smoking at age of 3, mother alcohol consumption during first trimester.