

META-ANALYSIS IN ALLERGY

Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis

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Summary

Background There is evidence to suggest that the risk of asthma might be increased with exposure to paracetamol in the intrauterine environment, infancy, later childhood and adult life.

Objective To review the evidence from studies investigating the association between paracetamol use in pregnancy and childhood asthma.

Methods A systematic review and meta-analysis was undertaken of studies reporting the association between paracetamol use in pregnancy and subsequent asthma in childhood. The primary outcome variable was wheeze in the last 12 months. For tabulated raw data, not adjusted for confounders, random effects odds ratios (OR) were pooled by the inverse variance weighted method.

Results There were six studies identified that were included in the meta-analysis. The age of children studied ranged from 30 to 84 months. The pooled random effects OR for the risk of current wheeze in the children of women who were exposed to any paracetamol during any stage of pregnancy was 1.21 (95% confidence interval 1.02–1.44). Features of the studies variably included an association with paracetamol use during all trimesters of pregnancy and an association with persistent asthma, severe asthma, and with atopy.

Conclusion and clinical relevance The use of paracetamol during pregnancy is associated with an increased risk of childhood asthma. More research is urgently required to determine the impact of paracetamol during pregnancy on the risk of wheezing in offspring so that appropriate public health recommendations can be made.

Keywords Asthma, childhood, paracetamol, pregnancy, systematic review

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Introduction

There is epidemiological evidence to suggest that the use of paracetamol may represent an important risk factor for the development of asthma, and its increasing use may have contributed to the increasing prevalence of asthma world-wide over the last 50 years [1, 2]. Associations have been observed between the risk of asthma and exposure to paracetamol in the intrauterine environment [3–10], infancy [5, 11], later childhood [11], adolescence [12], and in adult life [13–18].

A recent systematic review and meta-analysis [19] reported that the risk of asthma associated with paracetamol use in children and adults was 1.63 [95% confidence interval (CI) 1.46–1.77]. It also reported that pre-natal

paracetamol use by mothers was associated with an increased risk of asthma and of wheezing in children, with odds ratios (OR) of 1.28 (95% CI 1.16–1.41) and 1.50 (95% CI 1.10–2.05), respectively. However, the focus of the systematic review was not on the association with paracetamol use in pregnancy, the criteria for wheezing and asthma were not standardized between the studies, and the detailed findings of the studies were not presented.

To extend their report, we have undertaken a systematic review of studies investigating the association between pre-natal exposure to paracetamol and asthma in children, and have presented and discussed the findings in detail, including the magnitude of the association as determined by meta-analysis.

Methods

We conducted a systematic review and meta-analysis based on the guidelines outlined in *The PRISMA statement* [20].

Search strategy

We searched for articles written in any language using the health research databases Medline January 1950 to October 2010, EMBASE January 1947 to October 2010, Cochrane Database of Systematic Reviews 2005 to September 2010 and Cochrane Central Register of Controlled Trials 3rd quarter 2010. Studies were searched for using the keywords 'asthma' or 'wheeze' (and) 'acetaminophen' or 'paracetamol' (and) 'prenatal' or 'pregn\$'. There were no limits placed on the search. Search results were reviewed for relevance, and compared with previous meta-analysis for completeness [18] and the reference lists of the relevant studies were examined.

Study selection

Inclusion criteria. Studies that met the following criteria were included in the meta-analysis: published randomized-controlled trials (RCTs) and observational studies that involved the comparison of women who use/d paracetamol during pregnancy with a placebo (RCT) or control (observational) group and evaluated the effect of paracetamol use during pregnancy on offspring, using wheeze or asthma as a primary outcome (including abstracts). Only studies which presented raw data, or from which raw data was available from the authors on request, were used in the meta-analysis. In the situation where a study was published in different phases, that with the most complete raw data was included in the analysis.

Exclusion criteria. Studies were excluded sequentially based on the following criteria:

- publications that were reviews, commentaries, editorials or guidelines,
- studies in which asthma or wheeze were not primary or secondary outcomes,
- studies in which paracetamol use in pregnancy was not a primary (or secondary) exposure,
- studies that did not contain raw data for analysis.

Data abstraction

Two authors (S. E., R. B.) examined each paper's title and abstract and the full paper if necessary to determine if eligible for inclusion. Three authors (S. E., R. B., M. W.) independently examined selected publications for study quality and extracted raw data including age and number

of children with asthma or wheeze, number of women using paracetamol during pregnancy, trimester of pregnancy in which paracetamol use took place (if recorded) and amount of paracetamol used during pregnancy (if recorded). If appropriate data were not included in the studies, the lead author was contacted in an attempt to obtain the raw data. We noted that the included studies presented OR which were adjusted for multiple different potential confounders, and these differed considerably across the different studies. In addition, the tabulated raw data were not presented in relation to the potential confounders in stratified tables, therefore we were unable to adjust for a set of confounders common to all studies. Because of differing categorization of quantities of paracetamol used and timing of use during pregnancy, all stages of pregnancy were combined and exposure was dichotomized to use/no-use for the purpose of the meta-analysis. If data were presented for two age groups, the older age group was used for the purposes of the meta-analysis.

The primary outcome variable was wheeze in the last 12 months before interview, defined as 'current wheeze'.

Additional details relating to a potential dose-response relationship, or effect of family history or genetic status on the association with asthma, the potential effect of paracetamol use on atopic status, bronchial hyperresponsiveness and asthma severity, and the association with other antipyretics/pain relief medications were also recorded if available.

Statistical analysis

OR were pooled by the inverse variance weighted method. Fixed and random effects estimates were produced together with a homogeneity statistic and I^2 estimate. Publication bias was tested by the correlation coefficient between study size and estimate and by examination of a funnel plot. In the Forest plot the size of the boxes is inversely proportional to the variance for each study estimate.

Results

The outcome of the search strategy is shown in Fig. 1. There were six studies identified which met the criteria for inclusion in the meta-analysis [4, 5, 7–10]. The study characteristics are shown in Table 1. In the studies analysed, the age range of offspring was between 30 months and 84 months. For paracetamol use, the stage of pregnancy was combined in five studies [4, 7–10], however in one study [5], paracetamol use in pregnancy was split into early (0–20 weeks) and late (20–32 weeks) stages and the late pregnancy data were used for the analysis. In one study, use of paracetamol during pregnancy was

determined during the first and third trimesters and presented as combined data [8].

There was an increased risk of current wheeze in the offspring of women who were exposed to any paracetamol during any stage of pregnancy, with a pooled fixed effects OR of 1.20 (95% CI 1.11–1.29) and a pooled random effects OR of 1.21 (95% CI 1.02–1.44). Heterogeneity was present [homogeneity test χ^2 20.9, *df* = 5, P < 0.001, I^2

statistic 76.0 (95% CI 46.2–89.3)]. Because of the potential difficulty of pooling data from a cross-sectional study [9] with data from cohort studies, a sensitivity analysis was undertaken without the survey data and similar overall results were obtained, with a pooled fixed effects OR of 1.19 (95% CI 1.10–1.30) and a pooled random effects OR of 1.22 (95% CI 1.02–1.44). There was no evidence of publication bias (test for publication bias P = 0.85). The Forest plot is shown in Fig. 2. The individual findings of the included studies are described below.

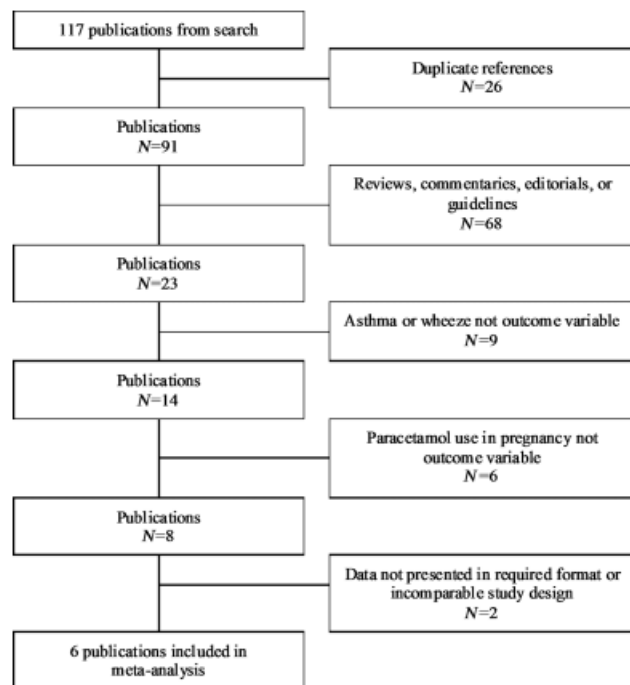


Fig. 1. Study flow based on the PRISMA statement [20].

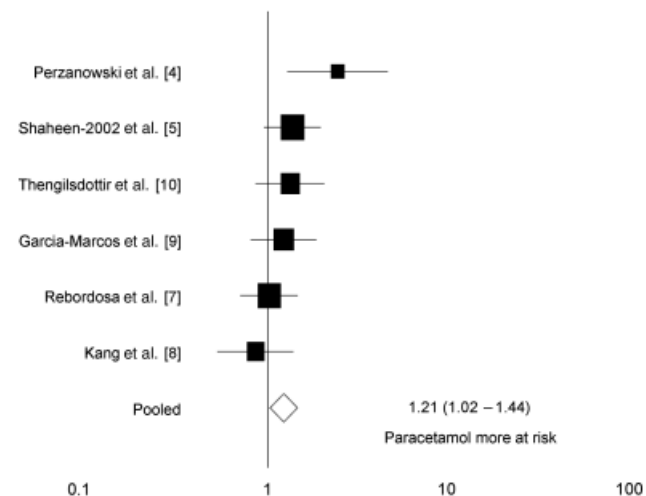


Fig. 2. Forest plot of the association between paracetamol use in pregnancy and asthma in childhood. For each study the box represents the random effects odds ratio and the line the 95% confidence intervals. The box size is inversely proportional to the variance (more precise studies have a larger box).

Table 1. Characteristics and findings from studies included in meta-analysis

Study [reference]	Design	Child age (months)	Paracetamol in pregnancy	Current Wheeze			Unadjusted OR (95% CI)
				Yes	No	Totals	
Perzanowski et al. [4]	Prospective cohort	60	Yes	38 (38.4%)	61	99	2.39 (1.40–4.06)
			No	41 (20.7%)	157	198	
Shaheen et al. [5]	Prospective cohort	30–42	Yes*	587 (15.4%)	3226	3813	1.35 (1.20–1.53)
			No	608 (11.8%)	4526	5134	
Thengilsdottir et al. [10]	Prospective cohort	54	Yes	83 (9.3%)	811	894	1.32 (1.01–1.72)
			No	193 (7.2%)	2485	2678	
Rebordosa et al. [7]	Prospective cohort	84	Yes	543 (8.0%)	6209	6752	1.01 (0.89–1.16)
			No	417 (7.9%)	4829	5246	
Kang et al. [8]	Prospective cohort	72	Yes	113 (65.7%)	59	172	0.85 (0.61–1.19)
			No	922 (69.2%)	411	1333	
Garcia-Marcos et al. [9]	Cross-sectional survey	36–60	Yes	194 (21.2%)	719	913	1.21 (0.95–1.54)
			No	147 (18.2%)	659	806	
						1719	

*Paracetamol use at 20–32 weeks in pregnancy.

Danish national birth cohort study

Rebordosa et al. [7] reported data from the Danish National Birth Cohort Study in which information was available on paracetamol use during pregnancy, and asthma symptoms in 66 445 infants at the age of 18 months and 12 733 children aged 7 years. Paracetamol use during pregnancy was associated with wheezing and with asthma, both at 18 months and at 7 years of age. The highest risk was observed for the association between persistent wheeze (children wheezing in the first 18 months of life as well as in the 12 months preceding interview at age 7) and paracetamol use in the first trimester of pregnancy (relative risk 1.35, 95% CI 1.02–1.78). At 18 months a significant association with wheeze was observed with paracetamol use during each of the three trimesters, although at age 7 years the association was significant for only first trimester paracetamol use. Use of paracetamol in the first trimester was also associated with severity of asthma attacks at age 7 years, measured as the number of wheezing attacks affecting sleep. There was no significant association between any measure of asthma, at either 18 months or 7 years of age, and pre-natal exposure to ibuprofen or aspirin in any trimester. Paracetamol was taken for pain by 91% of women studied, for fever in 16% and for muscle or joint disease in 20%.

Spanish infant survey

Garcia-Marcos et al. [9] reported data from a cross-sectional survey in which parents of 1741 children aged 3–4 years were interviewed. The focus of the study was the effect of asthma status of the mother on the association with wheezing in the preschool child. There was a significant association between the use of paracetamol by the mother at least once per month during pregnancy and risk of wheezing at preschool age (OR 1.71, 95% CI 1.15–2.53) but only amongst non-asthmatic mothers (OR 1.74, 95% CI 1.15–2.61). There was no association between prenatal paracetamol use and asthma in the offspring of asthmatic mothers, despite similar use of prenatal paracetamol to non-asthmatic mothers.

Dominican and African American birth cohort study

Perzanowski et al. [4] reported a birth cohort study undertaken in an inner city low income Dominican and African American population in the United States. In 301 children aged 5 years, prenatal paracetamol exposure predicted current wheeze (relative risk 1.71, 95% CI 1.20–2.42) and the risk increased monotonically with increasing number of days of prenatal paracetamol exposure. Exposure in the second and third trimester increased risk significantly, but the risk associated with use in the first trimester was of lesser magnitude and not statistically significant. An

increased risk associated with paracetamol exposure during pregnancy was also identified with persistent wheeze (relative risk 1.65, 95% CI 1.12–2.44), and ED visits for wheeze or difficulty breathing (relative risk 2.08, 95% CI 1.35–3.21). Prenatal paracetamol exposure predicted serological evidence of atopy (specific IgE antibodies ≥ 0.35 IU/mL to at least one allergen tested: *Dermatophagoides farinae*, mouse, cockroach, cat and dog) at age 5 years. The risk of wheeze and atopy was modified by the glutathione-S-transferase P1 (GSTP) gene, with a positive association observed only amongst children with the GSTP1 minor allele.

Avon longitudinal study of parents and children

Shaheen et al. [5, 6] reported the findings from the Avon Longitudinal Study of Parents and Children, a prospective cohort study of approximately 14 000 pregnancies and births, with data on the association of prenatal paracetamol exposure with wheezing at two ages in early childhood. Frequent use of paracetamol (most days/daily) in late (20–32 weeks) but not early (0–20 weeks) pregnancy was associated with increased risk of wheeze at age 30–42 months (OR compared with no use 2.10, 95% CI 1.30–3.41). Use in both early and late pregnancy was associated with significant increased risk of wheeze at 81 months (OR compared with no use of 1.81, 95% CI 1.05–3.13 and 1.86, 95% CI 0.98–3.55, respectively). There was a dose-response relationship demonstrated at both ages, and frequent use in late pregnancy was associated with increased risk of persistent wheezing but not transient infant wheezing. Aspirin use in early and late pregnancy was not associated with wheezing at either age. Use of paracetamol more than once in the first 6 months of life was associated with a small increase in the risk of wheezing at 30–42 months (OR compared with never use 1.29, 95% CI 1.05–1.57).

The ALSPAC study also reported the association with atopy assessed by skin prick testing to inhalant allergens and total serum IgE. There was an association between paracetamol use in late pregnancy and total IgE at 7 years, even after controlling for paracetamol and antibiotic use during infancy, although no association with skin prick test positivity.

United States cohort study

Kang et al. [8] reported data from a prospective study of 2379 pregnant women, with 1505 women interviewed when their children were 6 years old. Paracetamol was more likely to be used in pregnancy by women with diagnosed asthma (OR 1.56, 95% CI 1.24–1.96); overall, paracetamol was used by 69% of women during pregnancy. Use of paracetamol did not significantly increase the risk of asthma (OR 0.76, 95% CI 0.53–1.10).

Paracetamol use during both the first and third trimesters was associated with a significantly reduced risk of asthma (OR 0.59, 95% CI 0.36–0.98). There was no evidence of a dose–response relationship.

Western Sweden cohort study

Thengilsdottir *et al.* [10] reported a prospective, longitudinal cohort study of 8173 children in Sweden of whom 4496 completed followup at age 4.5 years. In the univariate analysis, they found an increased risk of overall wheezing disorder with both maternal allergy/asthma medication (OR 3.0, 95% CI 2.0–4.5) and paracetamol use (OR 1.5, 95% CI 1.03–2.2). In the multivariate analyses, only the association with maternal allergy/asthma medication remained statistically significant (OR 1.7, 95% CI 1.002–2.9). However, the risk of multiple-trigger wheeze was increased by paracetamol, both in the univariate and multivariate analyses (OR 2.3, 95% CI 1.3–4.2 and 2.4, 95% CI 1.2–4.9). The risk of episodic viral wheeze was not increased by paracetamol, neither in the univariate or in the multivariate analysis.

Studies not included in meta-analysis

Three other studies were identified in the systematic search but did not meet the criteria for inclusion in the meta-analysis.

Persky *et al.* [3] reported data from the Peer Education in Pregnancy Study, a controlled trial of a community-based education intervention; however, the raw data necessary for the meta-analysis was unable to be obtained. The study analysed 345 women in the first trimester of pregnancy and followed the offspring during their first year of life. There was a significant increased risk of wheeze in the first year of life in the offspring of mothers who used any paracetamol in mid- to late pregnancy (OR 1.8, 95% CI 1.1–3.0), but not early pregnancy (OR 1.0, 95% CI 0.6–1.6). Paracetamol use was also associated with a diagnosis of asthma and wheeze that disturbed sleep.

Bisgaard *et al.* [21] reported data from a birth cohort study, the Copenhagen Prospective Study on Asthma in Childhood, which was excluded from meta-analysis because the primary outcome was neonatal bronchial hyperresponsiveness and therefore not comparable to other study outcomes of childhood wheezing and/or asthma. Lung function and bronchial hyperresponsiveness to methacholine were measured in 404 neonates aged 6 weeks. Maternal intake of paracetamol during the third trimester was associated with a doubling of the bronchial responsiveness in the neonates, however this borderline significance was not maintained in the robust analysis eliminating outliers.

Koniman *et al.* [22] reported data from a matched patient-sibling case-control study undertaken in Singa-

pore. It was excluded because the variance estimate for the matched case-control study design was deemed to be incomparable to the unmatched data from the cross-sectional and cohort studies included in the meta-analysis. Paracetamol was used in pregnancy in six out of 17 children with allergic asthma, but in 0 out of 17 pregnancies of matched siblings without asthma ($P = 0.03$).

Discussion

The findings from this systematic review and meta-analysis support an association between any use of paracetamol at any stage in pregnancy and the risk of wheezing in offspring aged 2.5–7 years of age. The random effects OR for risk of asthma in offspring following paracetamol use in pregnancy, which takes into account the large degree of heterogeneity in the studies analysed, demonstrated a 21% increased risk, with the 95% CI ranging from a 2% to a 44% increased risk. Features of the studies variably included an association with paracetamol use within all trimesters of pregnancy, and associations with persistent asthma, severe asthma and atopy.

The strength of the association was similar to that reported by Etminan and colleagues [19], in which the OR for the risk of asthma and of wheezing with prenatal paracetamol use was 1.28 (95% CI 1.16–1.41) and 1.50 (95% CI 1.10–2.05). These similar estimates of risk were observed despite the methodological differences between the two meta-analyses. Etminan *et al.* [19] used adjusted OR or relative risks in preference to our approach of using raw data, and did not standardize the outcome variables. For example, the relative risk for ‘hospitalization for asthma’ was used in one study [7], the OR for wheezing in the offspring of non-asthmatic mothers (as opposed to all mothers) was used in another [9], and the OR from a third paper is not presented in the original manuscript [6]. Their measure of paracetamol use in pregnancy was variably frequent or any paracetamol use [19], whereas we standardized the primary outcome variable to wheeze in the last 12 months and paracetamol use to any use during pregnancy. We used data from the 7-year age group in the Rebordosa *et al.* study [7], whereas Etminan *et al.* [19] used data for the first year of life for which there was considerably greater power. We also included data from the Kang *et al.* [8] and the Thengilsdottir *et al.* [10] study which were not published at the time of the Etminan meta-analysis. These differences highlight the major difficulties and limitations in undertaking a systematic review and meta-analysis based on data from studies utilizing different methodologies. However, despite the methodological differences, the two meta-analyses have both shown a significant increased risk.

There are numerous other methodological issues that are also relevant to the interpretation of the findings. The

first is that the meta-analysis was conducted using raw, unadjusted data. Data from the individual studies were not presented in cross-tabulated form (stratified by individual potential confounders), which prevented us from adjusting for a group of confounders common to all included studies. It was also not possible to perform the meta-analysis using the reported adjusted OR, as each study controlled for multiple and varying confounders (one study [5] adjusted for 22 primary and seven secondary potential confounders) and, therefore, adjusted results were not comparable. As a result, it is possible that our results may be affected by confounding factors such as maternal smoking, respiratory disease in early life, gestational age, breastfeeding status, pet ownership and social class. Despite these possible confounding effects, our results are similar to those of Etminan and colleagues [19], who used adjusted results in their meta-analysis.

A second methodological issue is that the statistical test for heterogeneity was significant, although all but one of the studies had a confidence interval consistent with an association. The heterogeneity may be due to the different ages at which wheezing and asthma were measured, and potentially the varying doses of paracetamol used by mothers. We were unable to perform a meta-regression based on study level characteristics to explore this in more detail because of the small number of studies. Because raw data was used in the present analysis, the variability of confounders for which adjustment was made in the individual studies should not be a cause of the heterogeneity seen in our results.

Assessment of exposure to paracetamol in utero avoided the potential for confounding by indication, which represents the major source of potential bias in studies of paracetamol use in children [23–25]. This may occur in the situation of paracetamol being given for lower respiratory tract infections such as RSV or rhinovirus, which are associated with an increased risk of asthma in later childhood [26–28]. In addition, the observation that paracetamol was primarily used for pain during pregnancy and that indications for use did not modify the risk estimates suggests that the association is not likely to be due to confounding by indication. Furthermore, the finding that aspirin or ibuprofen use in pregnancy was not associated with an increased risk of asthma likewise suggests that the findings relating to paracetamol are not confounded by indication.

Wheeze in the last 12 months was chosen as the primary outcome variable instead of diagnosed asthma because it was recorded in all studies, it is known to carry good prognostic significance for asthma in this age group [29], and because the diagnosis of asthma is variable in young children. It could be argued that wheezing in the last 12 months may include some children who do not have clinically significant asthma. We addressed this in our review by examining the association with measures of

severe asthma such as wheezing attacks affecting sleep, medication use, ED visits, and hospital admissions for asthma. Using these criteria, a similar magnitude of risk was observed for both severe asthma and wheeze in the last 12 months [4, 7]. In addition, we restricted the analysis to data from the older age group in the Shaheen et al. [5, 6] and Rebordosa et al. [7] studies, in which findings were presented in different age groups in infancy and childhood.

The association of paracetamol use with persistent asthma is of interest due to the prognostic significance of this phenotype. Persistent asthma in which asthma symptoms are present throughout both infancy and early childhood, is a predictor of clinical asthma throughout later childhood [29, 30]. Three studies identified that the risk was strongest for persistent compared with either transient wheezing in infancy or late onset wheezing in childhood [4, 5, 7]. Furthermore in the Perzanowski et al. study [5], the association between prenatal paracetamol exposure and current wheeze strengthened as the children aged. In contrast, the study by Kang et al. [8] reported no association with paracetamol use and childhood wheezing, regardless of its classification as persistent wheezing or ever wheezing.

The observation that the association between paracetamol use in pregnancy and childhood asthma was only present in non-asthmatic mothers is important as it indicates that the association is not due to asthmatic mothers (being at greater risk of having a child with asthma) preferentially taking paracetamol due to aspirin avoidance [9]. This pattern of behaviour was suggested by the Kang et al. study in which it was observed that paracetamol was more likely to be used during pregnancy by mothers who had diagnosed asthma [8]. There is still a possibility however, that even among non-asthmatic mothers paracetamol use may have been associated with lower respiratory tract infections, which have been associated with poor lung function in offspring measured in early life [31] and hence wheezing or asthma-like symptoms.

It is unlikely that the association reported in the studies could be due to reporting bias, as the hypothesis that paracetamol use at any stage in life, including exposure in utero, may increase the risk of asthma is not widely known by asthma specialists, let alone the lay public. Another potential issue is confounding by paracetamol use in infancy, in that mothers who take paracetamol in pregnancy may be more likely to give paracetamol to their children. If this latter exposure is associated with childhood asthma, as suggested by the world-wide ISAAC study [11], then this could potentially confound the association observed with prenatal paracetamol exposure. This issue was considered in the Danish study, in which the association between paracetamol use during pregnancy and wheezing at 18 months remained significant when the analysis was restricted to children who had only

been exposed to the drug during pregnancy [7]. Furthermore, the use of paracetamol both pre- and post-natally was associated with a higher risk than only post-natal paracetamol use.

The association with prenatal paracetamol use may be present as early as 6 weeks of age as suggested by the findings from the Copenhagen prospective study of asthma in childhood [21]. In this study, mothers' use of paracetamol in the third trimester was associated with a doubling of bronchial hyperresponsiveness in the newborn, albeit with wide confidence intervals and failing statistical significance when outliers were removed in a robust test.

In some studies, a progressive increase in risk associated with increasing number of days of prenatal paracetamol exposure [4], or increased frequency of use [5, 6] was observed. However, a dose-response relationship was not observed by Kang *et al.* [8], or Rebordosa *et al.* [7], with the authors of the latter study proposing that the timing of exposure may be more important than the dose during pregnancy.

The effect of the timing of paracetamol use during pregnancy is relevant to the consideration of the potential mechanisms by which paracetamol may have an effect, if the association is causal. Glucuronidation, the main pathway for metabolism of paracetamol in adults, is markedly reduced in the foetus in the first trimester, whereas GST, which detoxifies the oxidative paracetamol metabolites, is reduced in the third trimester. The balance between these two pathways could determine whether paracetamol exposure in the first or third trimester increased the predisposition to subsequent asthma, through the build-up of toxic oxidative metabolites. This hypothesis would also invoke the concept of programming, in which an insult at

a crucial stage of foetal development may predispose to an increased risk of subsequent disease in childhood or adult life [32]. In the Danish study an association of paracetamol was greater with use in the first trimester, particularly with persistent wheeze in 7-year-old children [7]. In contrast, Persky *et al.* [3] and Perzanowski *et al.* [4] reported a greater risk for paracetamol use in the second and third trimesters and Shaheen *et al.* [5, 6] reported an effect with use after but not before 20 weeks of pregnancy. In contrast, Kang *et al.* reported no association between asthma and paracetamol use during either the first or third trimester of pregnancy [8].

The potential role of GST in the association between paracetamol exposure in utero and subsequent childhood asthma was suggested by the observation of Perzanowski and colleagues [4, 33] that the risk of wheeze was modified by GSTP1 genetic status. Prenatal paracetamol exposure predicted both current wheeze and seroatopy at 5 years among children with at least one copy of the GSTP1 minor allele (AG, GG) but not among children homozygous for the major allele (AA). GST is involved in the glutathione pathways and the minor allele has altered conjugation activity, potentially reducing the capacity of the foetus to metabolize paracetamol, leading to a build-up of toxic oxidative metabolites. The other potential mechanism is that paracetamol exposure may enhance developing Th2 responses [1, 2].

Conclusion

Given the findings of this as well as the previous systematic review and meta-analysis [19], we recommend further research into the impact of the use of paracetamol during pregnancy on the risk of wheezing in offspring.

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