

Prenatal paracetamol exposure and asthma: further evidence against confounding

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Background Observational studies have reported an association between maternal use of paracetamol in pregnancy and childhood asthma, which was not explained by measured confounding factors. However, it is possible that this relation might be confounded by unmeasured behavioural factors linked to paracetamol usage; if that were the case, effects of similar magnitude of partner's paracetamol use and/or postnatal maternal use would be expected.

Methods In the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based birth cohort, we compared the univariate effects of maternal use of paracetamol in pregnancy on risk of doctor-diagnosed asthma, wheeze and elevated immunoglobulin E (IgE) in the offspring at 7 years of age, with the univariate effects of partner's use and postnatal maternal use on these phenotypes.

Results Maternal use of paracetamol in pregnancy was strongly associated with all outcomes. Partner's use was very weakly associated with asthma but not associated with wheezing or IgE. Postnatal maternal use was associated with asthma and wheezing, though less strongly than was prenatal use, and was not associated with IgE. On mutual adjustment, the effects of maternal use in pregnancy on all outcomes were not substantially attenuated, whereas the effects of partner's use on asthma, and of postnatal maternal use on asthma and wheezing, were reduced.

Conclusions These findings suggest that the relation between maternal use of paracetamol in pregnancy and childhood asthma is unlikely to be confounded by unmeasured behavioural factors linked to paracetamol use.

Keywords Asthma, paracetamol (acetaminophen), prenatal exposure, confounding, ALSPAC, pregnancy, birth cohort

Introduction

There is increasing interest in the role of the prenatal environment in the aetiology of childhood asthma, and a number of prenatal risk factors have been

implicated.^{1–6} In a population-based birth cohort study, the Avon Longitudinal Study of Parents and Children (ALSPAC), we found that maternal use of paracetamol (acetaminophen) in late pregnancy was associated with an increased risk of early childhood

wheezing⁷ and of reported asthma and wheezing at 6 years of age and elevated total immunoglobulin E (IgE) at 7 years of age, but no increase in atopy.⁸ These associations remained after controlling for a large number of potential confounders. An association between prenatal paracetamol exposure and increased risk of early wheezing and later asthma has been confirmed in the Danish National Birth Cohort⁹ and a small US study recently reported an association with wheezing in infancy.¹⁰

Although these studies have controlled for a number of potential confounders, the possibility of confounding by unmeasured factors remains. If maternal use of paracetamol was simply a marker of other familial behaviours associated with childhood asthma one might expect to also see an association of similar magnitude with the equivalent exposure in the mother's partner or with postnatal use by the mother; partner's use during or after pregnancy could not have a direct biological effect on asthma risk in the child. However, if there was a direct biological effect of prenatal exposure, there should be a stronger effect of maternal use in pregnancy than of maternal postnatal use or of partner's use.¹¹ In the ALSPAC, partner's exposure has been used to address whether effects of maternal smoking in pregnancy on non-respiratory childhood outcomes are likely to be confounded. Effects of maternal smoking on birth weight¹¹ and offspring stature¹² were stronger than those of partner's smoking, supporting a causal effect of *in utero* exposure. In contrast, similar effects of partner's smoking were seen on offspring body mass index¹³ and blood pressure,¹⁴ suggesting that apparent effects of maternal smoking in pregnancy on these outcomes are confounded and are unlikely to reflect direct intrauterine effects.

In the ALSPAC cohort we have used a similar approach to compare the effects of maternal use of paracetamol in late pregnancy with the effects of postnatal use of paracetamol by the mother and her partner on doctor-diagnosed asthma, wheezing and elevated IgE in the child at 7 years of age.

Methods

The ALSPAC is a large population-based birth cohort established in the former county of Avon, UK, by recruitment of 14 541 pregnant women who were residents in Avon and had expected dates of delivery between 1 April 1991 and 31 December 1992. There were 14 062 live-born children. The study protocol has been described previously^{15,16} and further information is available on the ALSPAC website: <http://www.alspac.bris.ac.uk>. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee (IRB 00003312) and the Local Research Ethics Committees.

Exposures

Mothers were asked at 32 weeks of pregnancy how often they had taken paracetamol ('not at all, sometimes, most days, every day') during the previous 3 months. As very few mothers reported daily use, we combined this category with use on 'most days'. When the child was 61 months old the mother and her partner were asked how often they had taken paracetamol in the past year ('not at all, sometimes, often, every day'). As for use in pregnancy, the latter two categories were combined.

Outcomes

When the children were 7.5 years old, mothers were asked: 'Has your child had any of the following in the past 12 months: wheezing; asthma; eczema; hayfever?'. Children were defined as having current doctor-diagnosed asthma at 7.5 years of age if mothers responded positively to the question: 'Has a doctor ever actually said that your study child has asthma?', and positively to one or both of the questions on wheezing and asthma in the past 12 months. Serum total IgE (kU/l) was measured by fluorimmunoassay using the Pharmacia UNICAP system (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden).

Statistical analyses

Paracetamol exposures were analysed as univariate continuous effects, per frequency of use category, using regression (logistic for asthma and wheezing and linear on the logs for total IgE), and Huber variances throughout. For each outcome we first compared maternal prenatal use with maternal postnatal use, separately, and then controlling the effects for each other. Then we carried out similar analyses for maternal prenatal use vs partner's postnatal use.

Results

The univariate effect of maternal use of paracetamol in late pregnancy on doctor-diagnosed asthma in the offspring was stronger than the effect of postnatal use by the mother. After mutual adjustment, the effect of prenatal use remained stronger, with greater attenuation of the postnatal effect than the prenatal effect (Table 1). There was only very weak evidence for an effect of partner's use on asthma, and this effect was attenuated on adjustment for prenatal maternal use, whereas the latter effect changed little (Table 1). Comparison of maternal prenatal and postnatal effects on childhood wheezing gave similar results to those for asthma and there was no effect of partner's use on childhood wheezing (Table 2). Table 3 shows that whilst maternal use of paracetamol in pregnancy was strongly positively associated with total IgE in the offspring, neither postnatal use by the mother nor partner's use was associated with this outcome, and

Table 1 Comparison of effects of (a) maternal prenatal paracetamol use vs maternal postnatal use and (b) maternal prenatal paracetamol use vs partner’s postnatal use on asthma

Effect	OR (95% CI)	P
Doctor-diagnosed asthma		
Comparison (a) (n = 6926)		
Unadjusted		
Maternal prenatal	1.44 (1.25, 1.66)	2.9 × 10 ⁻⁷
Maternal postnatal	1.31 (1.12, 1.52)	0.0007
Mutually adjusted		
Maternal prenatal	1.39 (1.21, 1.61)	5.7 × 10 ⁻⁶
Maternal postnatal	1.21 (1.04, 1.42)	0.017
Comparison (b) (n = 3782)		
Unadjusted		
Maternal prenatal	1.50 (1.24, 1.82)	0.00003
Partner postnatal	1.17 (0.94, 1.46)	0.16
Mutually adjusted		
Maternal prenatal	1.49 (1.23, 1.81)	0.000043
Partner postnatal	1.13 (0.91, 1.42)	0.27

OR = odds ratio; 95% CI = 95% confidence interval.

Table 2 Comparison of effects of (a) maternal prenatal paracetamol use vs maternal postnatal use and (b) maternal prenatal paracetamol use vs partner’s postnatal use on wheezing

Effect	OR (95% CI)	P
Wheezing		
Comparison (a) (n = 7001)		
Unadjusted		
Maternal prenatal	1.40 (1.21, 1.63)	5.5 × 10 ⁻⁶
Maternal postnatal	1.22 (1.04, 1.43)	0.014
Mutually adjusted		
Maternal prenatal	1.37 (1.18, 1.59)	0.000032
Maternal postnatal	1.14 (0.97, 1.33)	0.12
Comparison (b) (n = 3821)		
Unadjusted		
Maternal prenatal	1.41 (1.15, 1.71)	0.00073
Partner postnatal	0.98 (0.78, 1.24)	0.87
Mutually adjusted		
Maternal prenatal	1.41 (1.16, 1.72)	0.00066
Partner postnatal	0.95 (0.76, 1.20)	0.69

consequently mutual adjustment did not attenuate the maternal prenatal effects.

Discussion

In this study we have demonstrated that strong univariate effects of prenatal exposure to paracetamol in

Table 3 Comparison of effects of (a) maternal prenatal paracetamol use vs maternal postnatal use and (b) maternal prenatal paracetamol use vs partner’s postnatal use on total IgE

Effect	GM ratio (95% CI)	P
Total IgE		
Comparison (a) (n = 4210)		
Unadjusted		
Maternal prenatal	1.20 (1.08, 1.32)	0.00035
Maternal postnatal	0.99 (0.89, 1.10)	0.84
Mutually adjusted		
Maternal prenatal	1.21 (1.09, 1.33)	0.00024
Maternal postnatal	0.95 (0.85, 1.06)	0.35
Comparison (b) (n = 2402)		
Unadjusted		
Maternal prenatal	1.22 (1.07, 1.39)	0.0026
Partner postnatal	1.01 (0.88, 1.17)	0.86
Mutually adjusted		
Maternal prenatal	1.22 (1.07, 1.39)	0.0026
Partner postnatal	1.00 (0.86, 1.16)	0.98

GM = Geometric Mean.

late gestation on doctor-diagnosed asthma, wheezing and total IgE at 7 years of age were stronger than, and not confounded by, partner’s paracetamol use or postnatal maternal use. This is most clearly demonstrated by the results for IgE. We have previously reported that the effect of prenatal paracetamol exposure on asthma phenotypes remained after controlling for a large number of potential confounders; although we did not have information on indications for use of paracetamol, effects of prenatal exposure persisted after controlling for maternal migraine, infections and antibiotic use in pregnancy, and for paracetamol use in infancy.^{7,8} These latest findings would suggest that the effects of prenatal exposure to paracetamol on asthma phenotypes are unlikely to be explained by unmeasured familial behaviours linked to paracetamol use and asthma. A similar approach, comparing maternal vs partner’s exposure, has been used previously in this cohort in a proof-of-principle study to demonstrate that the effect of maternal smoking in pregnancy on offspring birth weight is, as much other evidence attests, likely to be causal rather than confounded.¹¹ Although information on partner’s paracetamol use was collected when the child was 5 years old (and not during the pregnancy), this should not invalidate its use as an indicator of potential confounding by behaviour patterns common to mother and partner, which have not been measured. Partner’s use, whether during pregnancy or later, cannot have a direct causal effect on asthma risk in the child, and associated behaviours are likely to be similar, regardless of the timing of use.

Of potential concern is the fact that no data are available on indications for paracetamol use during pregnancy. However, the most common reasons are likely to be for headache and musculoskeletal complaints. We have no reason to believe the latter would confound relations with childhood asthma. Some mothers may have taken paracetamol for migraine, and there is some evidence that asthma may be more common in the offspring of mothers with migraine,¹⁷ but we controlled for a history of maternal migraine in our previous analyses.⁸ Pre-eclampsia is another potential confounder. This condition is associated with headaches and migraine,¹⁸ and women with pre-eclampsia who take paracetamol in late pregnancy are more likely to deliver babies preterm.¹⁹ Pre-eclampsia may also be associated with early childhood wheezing,⁶ though not with asthma,³ and with elevated IgE levels in the mother,^{20,21} which in turn are correlated with IgE levels in the offspring.²² However, pre-eclampsia is predominantly a condition of first pregnancies, and we controlled for parity in our previous analyses,⁸ as well as for low birth weight, which is associated with hypertension in pregnancy.

If the association between prenatal paracetamol exposure and asthma is causal, the underlying mechanisms remain to be clarified. We have previously suggested that paracetamol could plausibly promote Th2 responses. *In vitro*, paracetamol reduces intracellular glutathione (GSH) levels in human and animal alveolar macrophages and type II pneumocytes,^{23,24} and this in turn could drive Th2 cytokine responses.²⁵ Furthermore, oxidative stress and altered production of GSH may play a key role in the Developmental Origins of Health and Disease²⁶ by influencing epigenetic processes.²⁷ We therefore speculate that prenatal paracetamol exposure might influence asthma

development through epigenetic effects such as altered DNA methylation. In order to strengthen causal inference and shed light on possible mechanisms, we are investigating this possibility in the ALSPAC. We are also exploring whether the effects of prenatal paracetamol on asthma are modified by common antioxidant gene polymorphisms, as this would provide Mendelian randomization evidence regarding the causal nature of the paracetamol exposure.²⁸ Finally, given the recent report of a possible effect of infant paracetamol exposure on later asthma risk in a cross-sectional study,²⁹ we are investigating whether this relation can be confirmed prospectively, independent of prenatal exposure, in the ALSPAC.

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Conflict of interest: None declared.

KEY MESSAGES

- A number of studies have reported an association between maternal use of paracetamol in pregnancy and childhood asthma, which was not explained by measured confounding factors.
- If this relation was confounded by unmeasured familial risk factors linked to paracetamol usage, one would expect to also see effects of postnatal maternal use or partner's use of paracetamol, of similar magnitude.
- In the ALSPAC, a population-based birth cohort, maternal use of paracetamol in pregnancy was strongly associated with childhood asthma, wheezing and total IgE, but postnatal maternal use and partner's use were either less strongly, or not at all, associated with these outcomes.
- These findings suggest that the relation between maternal use of paracetamol in pregnancy and childhood asthma is unlikely to be confounded by unmeasured behavioural factors linked to paracetamol use.

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