ORIGINAL ARTICLE

Paracetamol use in pregnancy and wheezing in early childhood

S O Shaheen, R B Newson, A Sherriff, A J Henderson, J E Heron, P G J Burney, J Golding, and the ALSPAC Study Team

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See end of article for authors' affiliations

Correspondence to: Dr S Shaheen, Department of Public Health Sciences, Capital House, 42 Weston Street, London SE1 3QD, UK; seif.shaheen@kcl.ac.uk

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Background: We recently reported links between frequent paracetamol (acetaminophen) use and wheezing and asthma in adults and children, but data are lacking on possible effects of prenatal exposure on wheezing in early childhood.
Methods: In the population based Avon Longitudinal Study of Parents and Children (ALSPAC) women were asked twice during pregnancy (at 18–20 weeks and 32 weeks) about their usage of paracetamol and aspirin. Six months after birth, and at yearly intervals thereafter, mothers were asked about wheezing and eczema symptoms in their child. The effects of paracetamol and aspirin use in pregnancy on the risk in the offspring of wheezing at 30–42 months (n=9400) and eczema at 18–30 months (n=10 216) and on their risk of different wheezing patterns (defined by presence or absence of wheezing at <6 months and at 30–42 months) were examined.
Results: Paracetamol was taken frequently (most days/daily) by only 1% of women. After controlling for potential confounders, frequent paracetamol use in late pregnancy (20–32 weeks), but not in early pregnancy (<18–20 weeks), was associated with an increased risk of wheezing in the offspring at 30–42 months (adjusted odds ratio (OR) compared with no use 2.10 (95% CI 1.30 to 3.41); p=0.003), particularly if wheezing started before 6 months (OR 2.34 (95% CI 1.24 to 4.40); p=0.008). Assuming a causal relation, only about 1% of wheezing at 30–42 months was attributable to this exposure. Frequent paracetamol use in pregnancy was not associated with an increased risk of eczema. Frequent aspirin use in pregnancy was associated with an increased risk of wheezing only at <6 months.
Conclusions: Frequent use of paracetamol in late pregnancy may increase the risk of wheezing in the offspring, although such an effect could explain only about 1% of the population prevalence of wheezing in early childhood.

Oxidative stress in the pulmonary airways is thought to contribute to the pathogenesis of asthma by damaging airway epithelium, driving the inflammatory process, and promoting bronchial hyperresponsiveness (BHR).[1 2] Although antioxidants such as glutathione (GSH) offer some defence against reactive oxygen species generated by inflammatory cells in asthmatic airways,[3–5] this may be insufficient if dietary antioxidant intake is inadequate or if the oxidant burden is increased by inhaled pollutants or by drug metabolites.[6] Paracetamol (acetaminophen) is a potential source of oxidative stress, through production of its reactive metabolite, *N*-acetyl-*p*-benzoquinoneimine. In animal models paracetamol, in toxic doses, causes oxidative damage to airway epithelium[7] and may deplete the lung of GSH.[8 9] These observations led us to speculate that frequent use of paracetamol might, in susceptible individuals, cause oxidative stress in human airways and contribute to asthma symptoms. In a population based case-control study of adults we found a positive association between frequency of paracetamol use and asthma, asthma severity, and rhinitis.[10] Our subsequent ecological study showed that countries with higher paracetamol sales had higher prevalences of wheeze, asthma, rhinitis and BHR in adults, and higher prevalences of wheeze, allergic rhinoconjunctivitis, and atopic eczema in children and teenagers.[11] The findings for children prompted us to consider whether exposure to paracetamol in early life might influence the inception of atopic disease. As there are clues to suggest that the origins of atopy[12] and atopic disease[13] may lie in utero, we have investigated in a population based birth cohort whether use of paracetamol by mothers in pregnancy is associated with an increased risk of wheezing and eczema in their offspring in early childhood.

METHODS

The Avon Longitudinal Study of Parents and Children (ALSPAC)[14 15] is a prospective study of 14 541 pregnancies that resulted in 14 062 live births, of which 13 988 survived to 1 year. Women were enrolled as early in pregnancy as possible, on the basis of an expected date of delivery between 1 April 1991 and 31 December 1992, and place of residence within the three Bristol based health districts of the former county of Avon, UK. It was estimated, on the basis of actual deliveries between these dates, that 85–90% of eligible pregnant women were enrolled in the study.

Paracetamol use

Information on the use of paracetamol and aspirin during early pregnancy (before 18–20 weeks) was obtained from the following questions, asked at 18–20 weeks' gestation: "Please indicate how often you have taken the following pills during this pregnancy: aspirin; paracetamol . . ..". The options given were: every day; most days; sometimes; not at all. Information on the use of these analgesics in late pregnancy (20–32 weeks) was obtained from a questionnaire at 32 weeks' gestation which asked the same question about use in the previous 3 months. As only 0.2% of mothers reported daily use at 18–20 weeks, we combined this category with use on "most days". When the infant was 6 months old the mother was asked: "Please indicate which of the following have been given to your child in the past 6 months: paracetamol/Calpol" with the

Table 1 List of potential confounders included in the adjusted models

Potential confounder	Levels
Child's sex	Female*, male
Mother's education level	Below O level, O level only*, A level or higher, unknown
Mother's housing tenure	Owned/mortgaged*, council rented, non-council rented, unknown/other
Mother's ethnic origin	White*, non-white, unknown
Mother's parity	0*, 1, 2+, unknown
Mother's age (years)	<20, 20–24, 25–29*, 30–34, 35+
Birth season	January–March, April–June, July–September, October–December*
Breast feeding in first 6 months	No, yes*, unknown
Day care use in first 8 months	No*, yes, unknown
Antibiotic use in first 6 months	Never*, once, more than once, unknown
Mother's anxiety score in pregnancy (CCEI units)†	0–4*, 5–9, 10+, unknown
Pets kept in first year	No pets*, cat and/or dog, other pets only, unknown
Maternal smoking in pregnancy (cigarettes/day)‡	Not exposed*, passive only, 1–9/day, 10–19/day, 20+/day, unknown
Weekend tobacco exposure in first 6 months	Not exposed*, exposed, unknown
Mother's body mass index (BMI) (kg/m^2)	<20, 20–24.99*, 25–29.99, 30+, unknown
Crowding in home (persons/room)	Up to 1*, 1+, unknown
Damp and/or mould in home	No*, yes, unknown
Child's birthweight (g)	<2500, 2500–2999, 3000–3499*, 3500–3999, 4000+, unknown
Child's gestational age at birth (weeks)	<37, 37–40*, 41+
Multiple pregnancy	No*, yes
Child's head circumference (cm)	<33, 33–34.99*, 35–36.99, 37+, unknown
Child's birth length (cm)	<48, 48–50.99*, 51–53.99, 54+, unknown
Mother ever had asthma	No*, yes
Mother ever had eczema	No*, yes
Mother ever had rhinitis	No*, yes
Mother ever had migraine	No*, yes
Mother's atopic/migraine history unknown	No*, yes
Mother had cold/flu in late gestation	No*, yes
Mother had urinary infection in late gestation	No*, yes
Mother had other infections in late gestation	No*, yes
Mother's history of infections unknown	No*, yes

*Reference category.
†Subscale of the Crown-Crisp experiential index (CCEI) relating to free floating anxiety.
‡Maximum level of exposure reported by the mother in the questionnaires completed at 8 weeks, 18–20 weeks and/or 32 weeks gestation.

following possible responses: never; one episode only; two or more episodes.

Wheezing and eczema

Data on wheezing in the children were collected from questionnaires completed by mothers 6 months after birth and at 12 monthly intervals thereafter. Our primary outcome was wheezing at 30–42 months, determined from the response to the question asked at 42 months: "In the last 12 months has he/she had any periods when there was wheezing with whistling on his/her chest when he/she breathed?" A similar question at 6 months asked about wheezing since birth, and we used the information from these two time periods to identify four mutually exclusive groups of children: those who did not wheeze in either period ("non-wheezers"); those who wheezed before 6 months but not at 30–42 months ("transient infant wheezers"); those who wheezed at 30–42 months but not before 6 months ("later onset wheezers"); those who wheezed in both periods ("persistent wheezers"). Information on wheezing at both 6 and 42 months was complete for 9400 children.

The 12 month prevalence of eczema at 30 months was defined on the basis of a positive response to the question: "Has your child had an itchy dry skin rash in joints and creases of his/her body (e.g. behind the knees, under the arms) since he/she was 18 months old?".[16] Information was complete for 10 216 children. We chose to analyse eczema at 18–30 months because the questions asked below 1 year of age were thought to be less reliable for ascertaining true atopic eczema, and because after 18–30 months some children may "lose" their eczema (prevalence at 30–42 months was 4% lower).

Confounding factors and statistical analyses

Information on prenatal and postnatal potential confounding factors was collected from questionnaires completed during pregnancy and early childhood. The potential confounders included in the regression models are shown in table 1; many have "unknown" levels assigned to children for whom questionnaire data or birth measurements were incomplete. This minimised the loss of individuals with missing information from the analyses.

The primary exposures of interest were use of paracetamol in pregnancy and infancy. A secondary exposure of interest was use of aspirin in pregnancy, as this allowed us to examine whether any associations with prenatal paracetamol were specific or common to analgesics more generally. Adjusted and unadjusted odds ratios were calculated using the Stata statistical package[17] to fit binomial logistic regression models for wheezing and eczema and multinomial logistic regression models for the separate wheezing patterns (with non-wheezing as the base category), with robust confidence limits.[17] Adjusted odds ratios were preferred to adjusted relative risks because, when a complicated model is fitted, a logistic regression model is less likely to fail to converge. Population attributable fractions were calculated using the method of Greenland and Drescher.[18]

RESULTS

The distribution of selected background characteristics and paracetamol exposure of children who were and were not included in the main wheezing analyses were examined. The excluded children (who had incomplete wheezing data) were

Table 2 Odds ratios (95% CI) for wheezing at 30–42 months associated with paracetamol and aspirin use (n=9400)

	No. (wheeze/total)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Paracetamol use in pregnancy:			
0–20 weeks			
Never	516/4265	1.00	1.00
Some days	689/4836	1.21 (1.07 to 1.36)	1.07 (0.94 to 1.22)
Most days/daily	21/111	1.70 (1.04 to 2.75)	1.19 (0.72 to 1.97)
Unknown	32/188	1.49 (1.01 to 2.20)	1.47 (0.88 to 2.47)
20–32 weeks			
Never	608/5134	1.00	1.00
Some days	561/3725	1.34 (1.18 to 1.52)	1.12 (0.98 to 1.28)
Most days/daily	26/88	3.17 (1.99 to 5.05)	2.10 (1.30 to 3.41)
Unknown	71/453	1.40 (1.08 to 1.83)	0.58 (0.23 to 1.47)
Aspirin use in pregnancy:			
0–20 weeks			
Never	1150/8778	1.00	1.00
Some days	66/385	1.37 (1.05 to 1.80)	1.26 (0.95 to 1.68)
Most days/daily	12/65	1.50 (0.80 to 2.82)	1.05 (0.51 to 2.16)
Unknown	30/172	1.40 (0.94 to 2.09)	1.59 (0.90 to 2.82)
20–32 weeks			
Never	1145/8664	1.00	1.00
Some days	34/220	1.20 (0.83 to 1.74)	1.03 (0.71 to 1.51)
Most days/daily	8/63	0.96 (0.45 to 2.01)	0.64 (0.28 to 1.48)
Unknown	71/453	1.22 (0.94 to 1.58)	0.55 (0.22 to 1.37)
Paracetamol use in infancy:			
0–6 months			
Never	130/1245	1.00	1.00
Once	210/1860	1.09 (0.87 to 1.38)	1.06 (0.84 to 1.34)
More than once	916/6277	1.47 (1.21 to 1.78)	1.29 (1.05 to 1.57)
Unknown	2/18	1.07 (0.24 to 4.72)	–†

*Adjusted for factors in table 1.
†Could not be estimated.

more likely to have incomplete information on socio-demographic factors and paracetamol exposure. Among the children with complete information on these factors the excluded children were more likely to come from poorer socioeconomic backgrounds (as measured by mother's education, housing tenure, and crowding in the home), and to have mothers who were younger and who smoked in pregnancy (data not shown). The prevalence of maternal paracetamol use on most days/daily in late pregnancy was 1.5% in excluded children compared with 1.0% in those who were included in the analyses. Corresponding figures for paracetamol use more than once in infancy were 64.5% and 66.9%.

The 12 month prevalence of wheezing at 42 months was 13.4%. Table 2 shows the frequency of wheezing according to use of paracetamol and aspirin in pregnancy and of paracetamol in infancy, and the association between these exposures and wheezing. After controlling for potential confounding factors listed in table 1, there was no evidence for an association between paracetamol use in early pregnancy and wheezing at 30–42 months. For use in late pregnancy there was weak evidence for a small increase in risk associated with moderate use (on some days), however frequent use (most days/daily) was associated with a doubling in risk (adjusted odds ratio (OR) compared with never use 2.10 (95% CI 1.30 to 3.41); p=0.003). The proportion of wheezing at 30–42 months that was attributable to frequent paracetamol use in late pregnancy (population attributable fraction), assuming a causal relation, was 0.87% (95% CI 0.18 to 1.56).

Aspirin use in early and late pregnancy was not associated with wheezing at 30–42 months. 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 (adjusted OR compared with never use 1.29 (95% CI 1.05 to 1.57); p=0.01). The effect estimate for frequent use of paracetamol in late pregnancy did not decrease when we controlled additionally for paracetamol use in early pregnancy and in infancy.

Out of 9400 children with complete data, 6832 (72.7%) did not wheeze before 6 months or at 30–42 months (non-wheezers). There were 1310 children (13.9%) who wheezed before 6 months but not in the latter period (transient infant wheezers). Of 1258 children who wheezed at 30–42 months, 475 (5.1% of all children) had also wheezed before 6 months (persistent wheezers), and 783 (8.3% of all children) had not (later onset wheezers). Frequent paracetamol use in early pregnancy was not associated with any of the three wheezing patterns, but frequent use in late pregnancy was associated with an increased risk of persistent wheezing (adjusted OR compared with never use = 2.34 (95% CI 1.24 to 4.40); p=0.008, table 3). In contrast, frequent use of aspirin throughout pregnancy was associated with an increased risk of transient infant wheezing (adjusted OR for early pregnancy use 2.73 (95% CI 1.57 to 4.76), p=0.0004; OR for later pregnancy use 2.54 (95% CI 1.51 to 4.29), p=0.0005). There was weak evidence to suggest that use of paracetamol more than once in the first 6 months of life was associated with a small increase in risk of the transient infant and later onset patterns of wheezing, but stronger evidence for an increased risk of persistent wheezing.

The 12 month prevalence of eczema at 30 months in 10 216 children with complete data was 26.5%. Table 4 shows the relation between analgesic use and eczema. There was no evidence that paracetamol use in pregnancy was associated with eczema, and no clear evidence for an increased risk associated with aspirin use in pregnancy. There was a small increased risk of eczema associated with use of paracetamol more than once in the first 6 months of life (adjusted OR 1.22 (95% CI 1.05 to 1.41); p=0.009).

Table 3 Adjusted† odds ratios (95% CI) for wheezing patterns associated with paracetamol and aspirin use (n=9400)

	Transient infant wheeze* (n=1310)	Later onset wheeze** (n=783)	Persistent wheeze*** (n=475)
Paracetamol use in pregnancy:			
0–20 weeks			
Never	1.00	1.00	1.00
Some days	1.13 (0.99 to 1.29)	1.18 (1.00 to 1.38)	0.97 (0.78 to 1.19)
Most days/daily	1.45 (0.87 to 2.44)	1.18 (0.56 to 2.49)	1.41 (0.72 to 2.74)
Unknown	1.43 (0.78 to 2.63)	1.41 (0.72 to 2.74)	1.77 (0.80 to 3.91)
20–32 weeks			
Never	1.00	1.00	1.00
Some days	1.07 (0.93 to 1.22)	1.19 (1.01 to 1.40)	1.05 (0.85 to 1.30)
Most days/daily	0.88 (0.44 to 1.73)	1.72 (0.87 to 3.40)	2.34 (1.24 to 4.40)
Unknown	1.31 (0.48 to 3.58)	0.41 (0.21 to 0.82)	1.04 (0.22 to 4.95)
Aspirin use in pregnancy:			
0–20 weeks			
Never	1.00	1.00	1.00
Some days	0.86 (0.61 to 1.20)	1.13 (0.79 to 1.61)	1.43 (0.93 to 2.21)
Most days/daily	2.73 (1.57 to 4.76)	1.95 (0.90 to 4.20)	0.83 (0.22 to 3.19)
Unknown	1.38 (0.70 to 2.71)	1.61 (0.78 to 3.31)	1.86 (0.76 to 4.53)
20–32 weeks			
Never	1.00	1.00	1.00
Some days	0.86 (0.56 to 1.31)	0.83 (0.50 to 1.38)	1.33 (0.76 to 2.35)
Most days/daily	2.54 (1.51 to 4.29)	1.02 (0.39 to 2.62)	0.72 (0.19 to 2.70)
Unknown	1.29 (0.47 to 3.51)	0.38 (0.19 to 0.76)	1.00 (0.21 to 4.77)
Paracetamol use in infancy:			
0–6 months			
Never	1.00	1.00	1.00
Once	0.84 (0.66 to 1.06)	0.94 (0.72 to 1.24)	1.30 (0.84 to 2.00)
More than once	1.21 (0.99 to 1.48)	1.22 (0.97 to 1.54)	1.64 (1.13 to 2.39)

*Wheezing <6 months but not at 30–42 months.
**Wheezing at 30–42 months but not <6 months.
***Wheezing <6 months and at 30–42 months.
†Adjusted for factors in table 1 and compared with non-wheezers (no wheezing <6 months and at 30–42 months).

Table 4 Odds ratios (95% CI) for eczema at 18–30 months associated with paracetamol and aspirin use (n=10216)

	No (eczema/total)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Paracetamol use in pregnancy:			
0–20 weeks			
Never	1202/4565	1.00	1.00
Some days	1389/5246	1.01 (0.92 to 1.10)	0.99 (0.90 to 1.09)
Most days/daily	31/128	0.89 (0.59 to 1.35)	0.85 (0.56 to 1.30)
Unknown	89/277	1.32 (1.02 to 1.72)	1.51 (1.03 to 2.21)
20–32 weeks			
Never	1416/5469	1.00	1.00
Some days	1083/4022	1.05 (0.96 to 1.16)	1.04 (0.94 to 1.14)
Most days/daily	25/96	1.01 (0.64 to 1.60)	1.04 (0.65 to 1.66)
Unknown	187/629	1.21 (1.01 to 1.45)	1.13 (0.62 to 2.07)
Aspirin use in pregnancy:			
0–20 weeks			
Never	2483/9472	1.00	1.00
Some days	122/416	1.17 (0.94 to 1.45)	1.23 (0.99 to 1.53)
Most days/daily	24/69	1.50 (0.91 to 2.47)	1.42 (0.84 to 2.39)
Unknown	82/259	1.30 (1.00 to 1.70)	1.52 (1.01 to 2.29)
20–32 weeks			
Never	2432/9270	1.00	1.00
Some days	71/253	1.10 (0.83 to 1.45)	1.14 (0.85 to 1.51)
Most days/daily	21/64	1.37 (0.81 to 2.32)	1.27 (0.73 to 2.20)
Unknown	187/629	1.19 (1.00 to 1.42)	1.12 (0.61 to 2.04)
Paracetamol use in infancy:			
0–6 months			
Never	285/1279	1.00	1.00
Once	496/1916	1.22 (1.03 to 1.44)	1.17 (0.99 to 1.38)
More than once	1771/6416	1.33 (1.15 to 1.53)	1.22 (1.05 to1.41)
Unknown	159/605	1.24 (0.99 to 1.56)	–†

*Adjusted for factors in table 1.
†Could not be estimated.

DISCUSSION

In this population based follow up study we have found evidence to suggest that frequent use of paracetamol during late pregnancy may increase the risk of persistent wheezing, but not eczema, in the offspring in early childhood. We were testing, a priori, the hypothesis that exposure to paracetamol in early life might increase the risk of atopic disease. In contrast, the observation that frequent aspirin use in pregnancy may increase the risk of transient infant wheezing was unexpected. However, the p values suggest that the main findings are unlikely to have occurred by chance.

Bias and confounding

The population from which this cohort was drawn is broadly representative of the whole of Great Britain,[14 15] although the possibility that these findings might have arisen through bias or confounding needs to be considered. We excluded a third of the original birth cohort from the analyses of wheezing because information at both 6 months and 42 months was incomplete. These children differed from those in the analyses with respect to a number of socioeconomic and maternal factors and we cannot exclude the possibility that these exclusions biased the effect estimates for paracetamol. However, if the increased risk of wheezing associated with paracetamol was entirely spurious, frequent use in late pregnancy would have to have been strongly *protective* for wheezing among the excluded children, which seems unlikely. A potential limitation was the lack of more detailed information on frequency of paracetamol use in pregnancy. Use on "some days" will have encompassed a wide range of frequencies, and we lacked data on dosage and use of compound preparations containing paracetamol. Nevertheless, such misclassification is likely to be random with respect to wheezing in the offspring and would tend to lead to an underestimation of the magnitude of the effects. While mothers were not asked why they took analgesics on most days or daily in pregnancy, we think that indications for such frequent use would have included headache, migraine, and backache. There is some evidence that migraine and asthma are positively associated in adults,[19 20] and an asthmatic child is more likely to have a mother with asthma and with migraine.[21] However, a strong association between frequent paracetamol use in late pregnancy and wheezing in the offspring was present after controlling for a maternal history of asthma, other atopic diseases, migraine, infections in late pregnancy, and a considerable number of other prenatal and postnatal infections in late pregnancy, potential confounders in our analyses. Furthermore, exclusion of children with a maternal history of asthma from the analysis made little difference to the effect estimate for wheezing.

Wheezing phenotypes and specificity of effects

The Tucson study[22] and a more recent Italian study[23] have shown that childhood wheezing is heterogeneous in terms of associated risk factors and lung function abnormalities, depending on its age of onset and whether it persists beyond infancy. Using an analogous approach we have previously demonstrated comparable patterns of wheezing, with different associated risk factors, in early childhood.[24] In this study we found that frequent paracetamol use and frequent aspirin use in pregnancy were associated with different wheezing patterns. Aspirin exposure was of secondary interest to paracetamol exposure, and was included in our analyses to see whether associations with prenatal paracetamol use were specific for this particular analgesic or were associated with analgesic use more generally in pregnancy. Our observations indicate the former, and would suggest that, if the effects of frequent paracetamol and aspirin exposure are causal, they are likely to involve different mechanisms.

Possible mechanisms

In adult mice paracetamol in hepatotoxic doses can deplete the lung of GSH[8 9] and cause necrosis of the bronchiolar epithelium.[7 25 26] Clara cells are particularly vulnerable as in situ activation of paracetamol by cytochrome P450 occurs with production of the toxic metabolite.[25 26] Paracetamol crosses the placenta[27] and can be oxidised by fetal liver to generate this metabolite.[28] We suggest that heavy exposure in utero may cause oxidative damage to the bronchiolar epithelium and especially to its progenitor cell, the Clara cell, in the developing fetal lung. We speculate that this could "programme" the epithelial-mesenchymal-trophic unit which is involved in lung development and is thought to become reactivated[29] or to persist[30] in asthma, leading to BHR and persistent wheezing postnatally. The lack of an association with eczema would suggest that the relation between prenatal paracetamol exposure and wheezing is not mediated through an effect on atopy. Unexpectedly, the risk of childhood wheezing seemed to depend on the timing of prenatal exposure to paracetamol, with a clear effect of heavy exposure in late, but not early, gestation. This is in keeping with the hypothesis that programming occurs during critical periods of development,[31] and might reflect a greater vulnerability of the bronchial epithelium at this time. For example, expression of glutathione S-transferase (GST) which conjugates the toxic metabolite of paracetamol declines markedly in developing lung epithelium after 15 weeks of gestation, especially in distal airway epithelial cells.[32 33]

Transient infant wheezing is analogous to the transient early wheezing phenotype described in the Tucson study,[22] which is thought to occur with respiratory infections as a consequence of reduced airway calibre from birth, and which disappears as the airways grow and catch up in size. Hence, we speculate that the association between frequent aspirin use in pregnancy and this pattern of wheezing might indicate that aspirin has a detrimental effect on airway growth in utero which is not sustained postnatally. However, our interpretation is limited by a lack of information on dosage, and because we are not aware of possible mechanisms to explain such an effect.

Paracetamol use in infancy

Whilst in vitro work suggests that paracetamol could theoretically promote atopy through depletion of intracellular glutathione in macrophages[34] with consequent enhancement of Th2 cytokine responses,[35] we would recommend cautious interpretation of the associations between paracetamol use in infancy and subsequent wheezing and eczema for two reasons. Firstly, infants who have an atopic tendency from birth may be more likely to have eczema symptoms or wheezing with viral respiratory infections in the first 6 months of life which are severe and treated with paracetamol, and to have symptoms which persist beyond that age. Secondly, the majority of infants received paracetamol more than once in the first 6 months and the questions asked in infancy did not allow us to investigate relations with more frequent use.

Public health implications

We would emphasise that the proportion of women taking paracetamol or aspirin on most days or daily during pregnancy was very small (only 1% took paracetamol this frequently in late gestation). Consequently, the proportion of early childhood wheezing in the population that could be attributable to frequent use of these analgesics during pregnancy, assuming a causal relation, was also very small (about 1% attributable to frequent paracetamol use in late gestation). We recommend that paracetamol should remain the analgesic of choice in pregnancy, if used infrequently. Aspirin use in late pregnancy is generally discouraged because of the risk of premature closure of the fetal ductus arteriosus. We think that it would be prudent to avoid frequent use of aspirin in early pregnancy too.

Conclusions

The main findings of this prospective study add to our previous observations linking frequent paracetamol use to wheezing and asthma,[10 11] and to recent findings from the US which raise the possibility of an association between paracetamol use and asthma morbidity in children.[36] Our latest results suggest that heavy fetal exposure to paracetamol in late gestation may influence the inception of persistent wheezing in early childhood, thus lending support to the hypothesis that childhood asthma begins in utero, although the effect of this exposure on the prevalence of childhood wheezing in the population would be very small. Future work in this cohort will examine whether this exposure is associated with wheezing, asthma, atopy and BHR in later childhood, and whether the effects we have shown on early childhood wheezing are modified by genotype and antioxidant status.

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Authors' affiliations

S O Shaheen, R B Newson, P G J Burney, Department of Public Health Sciences, Guy's, King's and St Thomas' School of Medicine, King's College, London, SE1 3QD, UK
A Sherriff, A J Henderson, J E Heron, J Golding, Unit of Paediatric and Perinatal Epidemiology, Institute of Child Health, University of Bristol, BS8 1TQ, UK

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S Shaheen had the original idea for the study and wrote the draft paper. The study was designed by S Shaheen, J Henderson, J Golding and P Burney. A Sherriff carried out analyses of wheezing patterns before the study. J Heron carried out preliminary analyses related to paracetamol use in pregnancy. R Newson and S Shaheen carried out the main analyses. All authors contributed to interpretation of the data, revision of the paper, and approved the final version.

Conflicts of interest: none.

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