

REVIEW

The role of paracetamol in the pathogenesis of asthma

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Summary

Paracetamol use represents a putative risk factor for the development of asthma. There is convincing epidemiological evidence that the risk of asthma may be increased with exposure to paracetamol in the intrauterine environment, infancy, later childhood and adult life. A dose-dependent association has also been observed in these different age groups in different populations world-wide. An association has also been shown between paracetamol use in both rhinoconjunctivitis and eczema. There is biological plausibility with paracetamol use leading to decreased glutathione levels resulting in increased oxidant-induced inflammation and potentially enhanced T-helper type 2 responses. At the population level, patterns of paracetamol use might explain, to some extent, the world-wide variation in the prevalence of asthma and related disorders, particularly the high rates in English-speaking countries, which have high per capita prescription and over-the-counter use of paracetamol. A temporal association also exists between the international trends of increasing paracetamol use and increasing prevalence of asthma over recent decades. Further research is urgently required, in particular randomized-controlled trials (RCTs) into the long-term effects of frequent paracetamol use in childhood, to determine the magnitude and characteristics of any such risk. Importantly, RCTs will also enable evidence-based guidelines for the recommended use of paracetamol to be developed.

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Introduction

The reasons for the world-wide increase in the prevalence of asthma over recent decades and the international patterns of asthma prevalence are poorly understood and not adequately explained by the current knowledge of the causation of asthma [1]. This has led to the investigation of the role of novel risk factors that may increase the susceptibility to atopy and the development of asthma. One such risk factor for which there is evidence for a potential role in the pathogenesis of asthma is the use of paracetamol.

This hypothesis was first proposed 10 years ago when it was suggested that the change from the use of aspirin to paracetamol in children in the United States in the 1980s could have contributed to the increasing prevalence of childhood asthma noted in the United States during this period [2]. It was proposed that the substitution of paracetamol for aspirin may have led to an enhanced T-helper type 2 (Th2) immunological response, thereby increasing

the susceptibility to asthma and other allergic disorders. Since that time, there has been an increasing body of evidence to suggest that the use of paracetamol may represent an important risk factor for the development of asthma, and that its increasing world-wide use may have contributed to the increasing prevalence of asthma world-wide over the last 50 years [3–6]. This has led to recommendations that further research is urgently required, in particular randomized controlled trials (RCTs) into the long-term effects of regular paracetamol use [7, 8].

Intrauterine exposure (Table 1)

There have been six studies that have reported that the use of paracetamol in pregnancy is associated with an increased risk of childhood asthma (Table 1) [9–15]. In the population-based Avon Longitudinal Study of Parents and Children (ALSPAC), the frequent use of paracetamol in late pregnancy (20–32 weeks) was associated with a

Table 1. Paracetamol use in pregnancy and risk of childhood asthma

Country (reference)	Year of publication	Exposure in pregnancy	Comparison	Sample size (<i>n</i>)	Age of children	Outcome	Odds ratio (95% confidence interval)
United Kingdom ¹ [9]	2002	20–32 weeks	Most days/daily vs. no use	9400	3 years	Current wheezing	2.10 (1.30–3.41)
United Kingdom ² [10]	2005			8511	6–7 years		1.86 (0.98–3.55)
Denmark [11]	2008	During pregnancy	Ever use vs. no use	66 455	18 months	Wheezing ever	1.13 (1.10–1.17)
				12 733	7 years	Persistent wheezing	1.37 (1.07–1.75)
Singapore [12]	2007	During pregnancy	Ever use vs. no use	34	3–10 years	Allergic asthma	35% vs. 0%, <i>P</i> = 0.03
Spain [13]	2008	During pregnancy	At least once per month vs. no use	1741	3–5 years	Current wheezing	1.71 (1.15–2.53)
United States [14]	2008	During pregnancy	Ever use vs. no use	345	1 year	Current wheezing	1.8 (1.1–3.0)
United States [15]	2008	During pregnancy	Ever use vs. no use	280	5 years	Current wheezing	1.7 (1.2–2.2)

The superscript numbers refers to the order in which the assessment in this cohort study were undertaken at two ages.

twofold increased risk of wheezing in children at 3 years [9]. The frequent use of paracetamol in late pregnancy was associated with an increased risk of persistent wheezing [odds ratio (OR) compared with no use 2.34, 95% confidence interval (CI) 1.24–4.40], but not transient infant wheezing (OR compared with no use 0.88, 95% CI 0.44–1.73). This observation is significant as persistent wheezing is likely to progress to asthma in childhood, in contrast to transient infant wheezing, which is thought to occur with respiratory infections as a consequence of reduced airway calibre from birth and resolves in later childhood [16–19]. The observation that the effects appeared to depend on the timing of prenatal exposure to paracetamol is consistent with evidence that programming may occur during critical periods of fetal development [20].

The ALSPAC cohort was studied again when the children were 7 years old, with more detailed investigations including measures of atopy [10]. The use of paracetamol but not aspirin in late pregnancy was positively associated with asthma and total IgE (Table 1). However, there were no significant associations with skin prick test sensitivity, eczema or hayfever. The proportion of asthma attributable to paracetamol use in late pregnancy, assuming a causal relationship, was 7%. The authors concluded that paracetamol should not be used unnecessarily after 20 weeks' gestation.

In the Danish national birth cohort study, paracetamol was commonly self-administered during pregnancy, with a prevalence of use of 51% [11]. There was a small but statistically significant increased risk of diagnosed asthma at 18 months with paracetamol use during any time of pregnancy (Table 1) with ORs of 1.15 (95% CI

1.10–1.19), 1.13 (95% CI 1.09–1.18) and 1.17 (95% CI 1.13–1.22) for paracetamol use in the first, second and third trimesters, respectively. The association between paracetamol use during pregnancy and wheezing at 18 months remained significant when analysis was restricted to children who had been exposed to the drug only during pregnancy. The risk of hospitalization for asthma up to 18 months of age associated with paracetamol use during pregnancy was 1.24 (95% CI 1.11–1.38). Pain was the main reason for paracetamol use in pregnancy (91%) followed by fever (32%), musculoskeletal symptoms (20%), infection or inflammation (16%). Adjusting for indication did not modify the risk estimates for paracetamol use, nor did the estimates change when stratifying for indication of use. Risks for wheezing at 18 months among children whose mothers took only paracetamol during pregnancy were similar to those who took both paracetamol and aspirin. There was no general pattern of asthma risk associated with aspirin or ibuprofen use during pregnancy.

In a sub-analysis based on the older children in the cohort, use of paracetamol during pregnancy was also associated with an increased prevalence of doctor-diagnosed asthma at 7 years [11]. Similar to the findings from the ALSPAC cohort, the risk associated with the use of paracetamol during pregnancy was stronger for persistent wheezing (OR 1.37, 95% CI 1.07–1.75) than transient wheezing (OR 1.07, 95% CI 1.00–1.16). In contrast to the ALSPAC cohort, the magnitude of the risk with paracetamol use in the first trimester was similar to that for use in the third trimester.

A matched patient/sibling study from Singapore reported that the use of paracetamol during pregnancy was

associated with allergic asthma in childhood (Table 1) [12]. A positive association was also noted between paracetamol consumption in the first 6 months of life and asthma.

A Spanish cohort study has reported that frequent paracetamol use in pregnancy was associated with wheeze during pre-school years, but only among children of non-asthmatic mothers (OR 1.74, 95% CI 1.15–2.61) (Table 1) [13]. This observation is important as it indicates that the association could not be due to mothers with asthma using paracetamol in preference to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs), to avoid NSAID-induced bronchospasm.

Recently, two cohort studies from the United States have also reported an association between *in utero* exposure to paracetamol and asthma in childhood [14, 15]. In one study, the use of paracetamol in middle to late, but not early pregnancy, was significantly related to wheezing in the first year of life (OR 1.8, 95% CI 1.1–3.0) [14]. In the other study [15], which was based in an inner-city minority community, prenatal paracetamol use was significantly associated with current wheeze at 5 years (OR 1.7, 95% CI 1.2–2.4). Third trimester paracetamol use had the strongest association with current wheeze. Paracetamol use in pregnancy was common in this Dominican and African-American community, being reported by 36% of mothers. However, in another birth cohort study, maternal paracetamol use in pregnancy was not associated with an elevated total IgE in cord blood or in 6- and 12-month-old infants [21].

Paracetamol use in infancy

In ALSPAC, the use of paracetamol more than once in the first 6 months of the infants life was also associated with

an increased risk of wheezing at 3 years (OR vs. no use 1.29, 95% CI 1.05–1.57) [9]. The risk with paracetamol use in infancy was particularly evident for persistent wheezing, rather than transient infant wheezing. Paracetamol was frequently administered to infants, with about two-thirds of all infants having received paracetamol more than once in their first 6 months of life. A New Zealand study extended these observations by reporting a link between paracetamol use in infancy and asthma at age 6–7 years [22]. However, an Australian longitudinal birth cohort study reported that although the frequent use of paracetamol is associated with an increased risk of childhood asthma (OR 1.85, 95% CI 1.18–2.89), the effect was confounded by early respiratory infections (adjusted OR 1.30, 95% CI 0.78–2.19) [23, 24]. In the United States inner-city study discussed above [15], there was no association between post-natal paracetamol use at age 1, 2 or 3 years and subsequent wheeze at 5 years.

Evidence for an association between paracetamol use in infancy and asthma in childhood also comes from Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC), which included data from around 200 000 children from 73 centres in 31 countries [6]. In the multivariate analyses, the reported use of paracetamol for fever in the first year of life was associated with an increased risk of current asthma symptoms (wheeze in the last 12 months) at age 6–7 years (OR 1.46, 95% CI 1.36–1.56) (Table 2a). The association was present in countries throughout the world, with different patterns of childhood febrile illnesses and differences in medical practice and over-the-counter medication use. A similar association was noted with the use of paracetamol for fever in the first year of life and severe asthma symptoms, a symptom complex used to identify children with clinically significant asthma. The population-attributable risk

Table 2. The ISAAC Study: the association between the use of paracetamol (a) in the first year of life, (b) at age 6–7 years, and the risk of current symptoms of asthma, rhinoconjunctivitis and eczema in 6–7-year-old children [6]

		Odds ratio (95% confidence interval)
<i>(a) Paracetamol use for fever in first year of life</i>		
Wheeze in last 12 months		1.46 (1.36–1.56)
Severe asthma symptoms in last 12 months		1.43 (1.30–1.58)
Rhinoconjunctivitis symptoms in last 12 months		1.48 (1.38–1.60)
Eczema symptoms in last 12 months		1.35 (1.26–1.45)
		Odds ratio (95% confidence interval)
	Medium vs. none	High vs. none
<i>(b) Paracetamol use in last 12 months</i>		
Wheeze in last 12 months	1.61 (1.46–1.77)	3.23 (2.91–3.60)
Severe asthma symptoms in last 12 months	1.33 (1.15–1.53)	3.54 (3.05–4.11)
Rhinoconjunctivitis symptoms in last 12 months	1.32 (1.20–1.46)	2.81 (2.52–3.14)
Eczema symptoms in last 12 months	1.18 (1.08–1.30)	1.87 (1.68–2.08)

ISAAC, International Study of Asthma and Allergies in Childhood.

of severe asthma symptoms due to paracetamol use in infancy was 22%.

An important consideration was the extent to which the findings may have been due to confounding by indication. This may occur in the situation of paracetamol being given for lower respiratory tract infections due to respiratory syncytial virus and rhinovirus, which are associated with an increased risk of asthma in later childhood [25, 26]. It is also relevant that episodes of fever in infancy are associated with a reduced risk of asthma with allergic sensitization at age 6–7 years [27, 28]. This association is both intensity dependent and frequency dependent, with progressive reductions in risk with a greater maximum recorded temperature beyond 38 °C and with increasing number of febrile episodes. It is possible that paracetamol taken for high fever would, by association, be linked to a reduced risk of subsequent asthma. Alternatively, the antipyretic action of paracetamol could potentially contribute to an increased risk of asthma, by reducing the protective effect of fever. Thus, the extent to which confounding by indication may have contributed to the association between paracetamol and asthma in the ISAAC study is uncertain [24]. Furthermore, the presence of confounding does not exclude the possibility of a co-existing causal relationship [8].

In the ISAAC analyses, an increased risk of rhinoconjunctivitis and eczema was also observed with paracetamol use in infancy, suggesting that the effect of paracetamol is not restricted to the airways (Table 2a).

Paracetamol use in childhood

The sole RCT of paracetamol use in asthma was undertaken in asthmatic children aged 6 months–12 years who received an asthma medication daily and were not known to be sensitive to aspirin or other NSAIDs [29]. Asthmatic children who had a febrile illness were randomly assigned to receive either paracetamol or ibuprofen for fever control. Children randomized to ibuprofen had a reduced risk of an outpatient visit for asthma (OR 0.56, 95% CI 0.34–0.95) and hospital admission for asthma (OR 0.63, 95% CI 0.25–1.26). The reduced risk of outpatient visits associated with the use of ibuprofen was observed with the treatment of fever due to respiratory (OR 0.43, 95% CI 0.24–0.79) but not other infective causes (OR 0.93, 95% CI 0.44–2.0). There was also a dose-response effect noted, with a higher cumulative incidence associated with paracetamol doses ≥ 11 mg/kg than lower doses (6.3% vs. 4.4%, respectively). The findings of this study indicate that paracetamol may have a role in increasing the severity of exacerbations in existing disease, in addition to a role in its pathogenesis. Because the study did not include a placebo treatment, it was not possible to determine whether the observed difference in morbidity according to treatment group was attributable to an

increased risk with paracetamol or a decreased risk with ibuprofen. This consideration is important as there is evidence that NSAIDs may have some protective effect against the development of asthma [2, 7, 30–32].

The main epidemiological evidence of an association between paracetamol use in children and current asthma symptoms comes from Phase III of the ISAAC programme [6]. In addition to reported paracetamol use in infancy, reported current paracetamol use in the 6–7-year-old children was also recorded and the association with current asthma symptoms was determined. In the 6–7-year-old children, the reported current use of paracetamol was associated with a dose-dependent increased risk of current asthma symptoms (OR 1.61, 95% CI 1.46–1.77 and 3.23, 95% CI 2.91–3.60) for moderate and high vs. no use, respectively (Table 2b). There was also a dose-dependent increased risk of severe asthma symptoms. Paracetamol use in infancy and at age 6–7 years was linked, with parents who administered paracetamol to their infant more likely to administer paracetamol in later childhood. However, the risk with paracetamol for fever in childhood was present independently of paracetamol use for fever in the first year of life and vice versa. Similar dose-dependent associations were obtained between current paracetamol use and current symptoms of rhinoconjunctivitis and eczema.

The findings relating to current paracetamol use in childhood are unlikely to be influenced by confounding by indication; however, it would be prone to reverse causation if children with asthma were more likely to develop febrile episodes and as a result have greater paracetamol use. However, this would not hold for the observed association between paracetamol use and eczema, independent of asthma, as the symptoms and complications of eczema are not typically associated with the use of paracetamol.

Paracetamol use in adults

A population-based case-control study of dietary antioxidants and asthma from the United Kingdom also collected information on the use of analgesics [33]. In adults aged 16–49 years, there was a dose-dependent association between paracetamol use and asthma, with a 2.4-fold increased risk in daily users (Table 3). Another finding was that among cases, daily paracetamol use was associated with more severe disease, with ORs of 1.35 (95% CI 0.55–3.34), 2.25 (95% CI 0.90–5.66) and 8.15 (95% CI 2.84–23.40) for mild, moderate and severe asthma, respectively. These observations suggest that paracetamol may play a role in increasing the severity of asthma. The association with paracetamol use was present in both users and non-users of aspirin, and the frequency of aspirin use was not associated with asthma, or asthma severity, suggesting that the association of paracetamol

Table 3. The use of paracetamol and dose-dependent risk of current asthma in adults

Paracetamol use	Odds ratio (95% confidence interval)
<i>(a) United Kingdom, risk of current asthma symptoms*</i> [33]	
Never	1.0
< monthly	1.06 (0.77–1.45)
Monthly	1.22 (0.87–1.72)
Weekly	1.79 (1.21–2.65)
Daily	2.38 (1.22–4.64)
<i>(b) Ethiopia, risk of current wheezing†</i> [34]	
Never	1.0
1–3/month	1.26 (1.06–1.50)
> 3/month	1.89 (1.51–2.36)
<i>(c) United States, risk of diagnosed asthma‡</i> [36]	
Never	1.0
Occasional (1–5 times/month)	1.15 (0.99–1.34)
Regular (6–29 times/month)	1.40 (1.12–1.75)
Daily (≥ 30 times/month)	1.75 (1.34–2.28)

*Defined by positive responses to questions about asthma attacks, asthma medication, or waking at night with shortness-of-breath.

†Defined by wheezing or whistling in chest at any time in the last year.

‡Asthma was defined as self-report of ever having physician-diagnosed asthma.

with asthma was not due to aspirin avoidance by asthma patients.

In a survey of adults and children in Ethiopia [34], allergic symptoms increased significantly with the frequency of paracetamol use, with ORs of those using more than three tablets in the last month relative to no use of 1.89 (95% CI 1.51–2.36) for wheeze, 2.52 (95% CI 1.99–3.2) for rhinitis and 1.90 (95% CI 1.35–2.61) for eczema (Table 3). The findings from the nested case-control study suggested that the dose-related associations between paracetamol use and asthma symptoms could not be attributed to aspirin avoidance or reverse causation. This interpretation was based on the observations that only 1% of cases reported avoiding aspirin, none took paracetamol for asthma symptoms and because children under the age of 5 years who commonly experience viral-induced wheeze were excluded. The lack of difference in paracetamol consumption between urban and rural areas included in the study suggested that use was not related to a more western lifestyle in the urban population.

In the United States Nurses Health Study [30], increasing frequency of paracetamol use was positively associated with newly diagnosed (adult-onset) asthma over a 7-year period. The multivariate rate ratio for asthma for participants who received paracetamol for > 14 days per month was 1.63 (95% CI 1.11–2.39) compared with non-users. The positive association of paracetamol use and asthma did not differ significantly between participants who did and did not receive aspirin. Paracetamol was commonly used in this cohort, with about 20% taking

paracetamol at least 5 days per month and 5% > 22 days per month.

Similarly, in a cohort study of adult twins enrolled in the nationwide Danish Twin Registry, a higher prevalence of new-onset asthma over an 8-year period was reported in subjects with frequent intake of paracetamol (OR 3.03, 95% CI 1.51–6.11) [35]. Adjustment for frequent intake of medications other than paracetamol showed a small reduction in effect size (OR 2.16, 95% CI 1.03–4.53) consistent with some degree of confounding with other medications and diseases. Restricting the analysis to include only twin pairs discordant for frequent paracetamol intake showed a similar point estimate of risk although not reaching statistical significance (OR 2.00, 95% CI 0.37–10.92).

In a cross-sectional analysis using the US Third National Health and Nutrition Examination Survey [36], there was a dose-dependent association of paracetamol use and asthma (Table 3). There was also an association with chronic obstructive pulmonary disease (ORs 1.16, 95% CI 1.09–1.24) and an inverse association with forced expiratory volume in 1 s, with a reduction of 54.0 mL (95% CI 90.3–17.7 mL) when daily users were compared with never users. The specificity of the association with paracetamol (not aspirin or ibuprofen) and the dose-response relationship provided support for a causal relationship. The study also observed a strong association between paracetamol use and asthma in the subgroup of subjects with non-atopic asthma.

As part of a multi-centre case-control study organized by the Global Allergy and Asthma European Network, the association between frequent paracetamol use and adult asthma was examined in 12 European centres [37]. Weekly paracetamol use, when compared with less frequent use, was positively associated with asthma, and the overall effect estimate became stronger after controlling for confounders (adjusted OR 2.87, 95% CI 1.49–5.37) (Fig. 1). No significant heterogeneity in risk was observed between the centres, and no association was seen between the use of other analgesics and asthma. Information was not collected on indications for use and although it is possible that some cases were taking paracetamol for conditions such as migraine, which is more frequently experienced in people with asthma [38, 39], it is unlikely to confound the association between paracetamol and asthma to a substantive degree, as migraine is uncommon even in asthmatics. In support of this interpretation, the previous UK case-control study reported that frequent paracetamol was taken for migraine in only 0.02% of asthmatics and 0.01% of non-asthmatics [30].

Ecological analyses

The international ecological analyses based on data from countries participating in ISAAC Phase I and the European

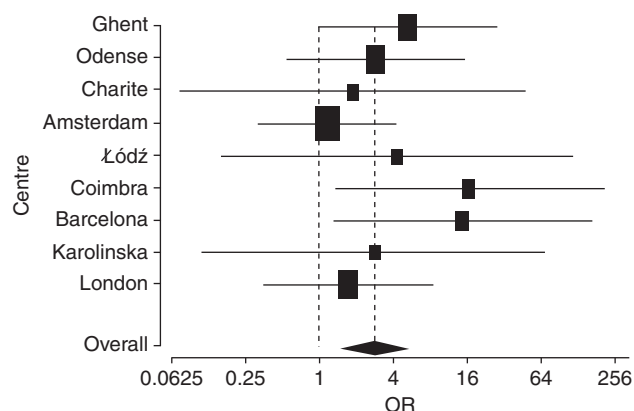


Fig. 1. Forest plot showing meta-analysis of asthma risk according to weekly paracetamol use (vs. less than weekly use). Data are presented as adjusted odds ratios [ORs ■ (size reflects weighting)], using a random effect model, and 95% confidence intervals (horizontal bars). The line of no effect is shown (.....). The centre of the diamond indicates the combined mean effect of the studies (OR 2.87; - - - - -), and the extremities of the diamond shows the 95% confidence interval (Shaheen et al. [37]).

Community Respiratory Health Survey have identified positive associations between per capita consumption of paracetamol and the prevalence of asthma in children and adults, respectively [40]. It was calculated that the prevalence of wheeze increased by 5.2% in 13–14-year-olds and by 2.6% in adults for each 10 gm per year increase in per capita paracetamol sales. Interestingly, English-speaking western countries, which have among the highest prevalence rates of asthma, also have some of the highest per capita paracetamol sales. This observation suggests that higher paracetamol usage may explain some of the higher prevalence of asthma in English-speaking countries, particularly in children.

Time trends

Internationally, the increasing use of paracetamol over the last 50 years has occurred contemporaneously with the increasing prevalence of asthma in countries from different regions of the world. Paracetamol was marketed internationally in the 1950s, with a progressive increase in sales, particularly in children, to the extent that in the United States they matched those for aspirin by 1980 (Fig. 2) [41]. Because of concerns about the risk of Reye's syndrome with aspirin use, paracetamol sales increased markedly throughout the 1980s to the extent that it had almost completely replaced aspirin as the analgesic and antipyretic of choice in infants and children in the United States by 1990 [2]. At this stage, paracetamol had become the most commonly dispensed medication in the United States, representing 5% of all treatments [42]. These trends of increasing use of paracetamol in children have been

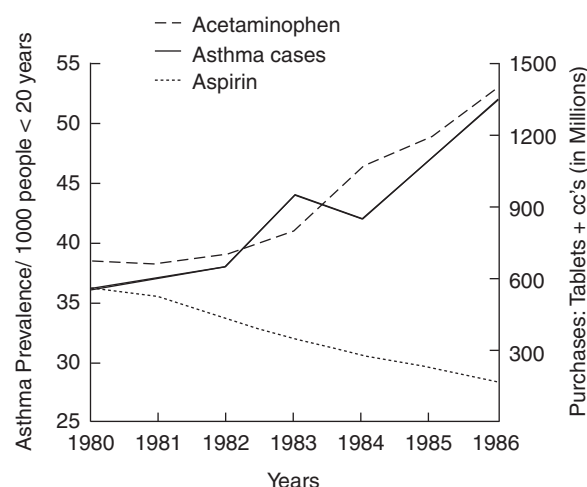


Fig. 2. Prevalence of asthma in people under the age of 20 years and (—) total drug store purchases of paediatric aspirin (.....) and paracetamol (- - - -) in the United States from 1980 to 1986 (Varner et al. [2]).

temporally associated with an increase in the prevalence of asthma in many countries world-wide [1].

There are likely to be many reasons for the frequent reported use of paracetamol by both children and adults, including its efficacy in relieving fever and pain, safety when used in recommended doses and its availability as an over-the-counter medication. Another factor may relate to the analgesic effect of paracetamol being due to the indirect activation of cannabinoid CB₁ receptors in the brain and spinal cord [43, 44]

Potential mechanisms

There are several mechanisms that have been proposed to explain why paracetamol use may increase susceptibility to asthma and other allergic disorders. The main mechanism is that paracetamol may impair respiratory antioxidant defences by decreasing the amount of reduced glutathione present [45–48]. Oxygen radicals may produce tissue injury [49], smooth muscle contraction [50] and bronchial hyper-responsiveness [51], increased vascular permeability [52], release of pro-inflammatory mediators [53, 54] and impaired β -receptor function [55], all effects potentially relevant to the pathogenesis of asthma. Depletion of antioxidants such as glutathione has the potential to impair the protection against these injurious effects of oxygen radicals, resulting in airways' inflammation [56].

Glutathione is present in increased concentrations in alveolar fluid of patients with asthma, and an association exists between levels of glutathione and the degree of bronchial hyperresponsiveness [57]. These data suggest that patients with asthma have increased antioxidant defences, which may balance an increase in oxygen radical generation, which has been observed in patients

with asthma [58]. During exacerbations of asthma, glutathione levels are low, increasing again during recovery [59].

Another mechanism relates to the modulating effect of glutathione levels on Th1–Th2 cytokine response patterns [48, 60]. Depleting glutathione in antigen-presenting cells *in vitro* and *in vivo* in animal models causes a shift away from Th1 to Th2 cytokine production that could pre-dispose to atopic diseases such as asthma. These mechanisms are likely to result from gene/environment interactions, as genetic polymorphisms of the glutathione-S-transferase family of genes influence asthma predisposition [61, 62].

Another possible mechanism is that by reducing fever, paracetamol use may reduce the cytokine storm that occurs as part of the febrile response. The prevalent cytokines released during a fever include IFN- γ and IL-2, which have predominant Th1 profiles. However, while paracetamol reduces fever, there is conflicting evidence as to whether it also influences the pattern of cytokine production [63, 64], and its effect on cytokines may depend on the cause of the fever. A further potential mechanism is that paracetamol may influence COX-2 activity and the production of prostaglandin E2 [2].

Future research

Further research is urgently required and in particular, RCTs need to be undertaken into the long-term effects of the use of paracetamol at different stages in life to determine the magnitude and nature of any risk. It would be problematic from an ethical perspective to undertake RCTs of the effect of exposure to paracetamol *in utero*. It could be argued that sufficient evidence exists from the epidemiological studies undertaken to date that paracetamol use in pregnancy increases the risk of the child subsequently developing asthma and to therefore recommend that paracetamol use in pregnancy is limited. This would be consistent with the principle of limiting the use of all medications in pregnancy to definite indications where the benefits markedly outweigh the risks to both the mother and fetus.

The priority for RCTs is to examine whether paracetamol use in early childhood influences the risk of developing asthma in later childhood. Ideally, this would involve the comparison of the use of paracetamol vs. placebo; however, this would be difficult to undertake due to the firmly held belief of parents and doctors in many countries that an antipyretic must be administered to a febrile child to reduce morbidity and the risk of febrile convulsions. This belief is held despite data that suggest that paracetamol does not have major clinical benefits in the treatment of young children with fever [65, 66], and that this treatment approach does not reduce the risk of febrile convulsions [67, 68]. The observation that in many

countries paracetamol is frequently administered (e.g., just under 20% of the parents of 6–7-year-old children in the ISAAC study reported that their child using paracetamol at least once a month in the last year) [6] suggests that a liberal vs. a restricted paracetamol use regime could be compared. This would have the advantage in terms of generalizability, with current practice of liberal use compared with restricted use (i.e. in the situation of a fever $>38.5^{\circ}\text{C}$) as recommended in current WHO guidelines [69]. Another approach would be to compare paracetamol with ibuprofen as undertaken in the previous RCT of asthmatic children [29]. While the interpretation of the findings would be limited in the respect that it would not be possible to determine which medication had an effect, if a difference was observed, the findings would still be generalizable to clinical practice and allow recommendations of a preferred agent to be made. The other methodological approach that could be undertaken is an RCT of paracetamol in children recruited at the time of a hospital admission with bronchiolitis. This study design would have advantages in terms of study recruitment, requiring fewer participants due to the high rate of subsequent asthma in children who have experienced a previous episode of bronchiolitis requiring hospital admission [70–72].

In adults, the opportunity exists to investigate whether the regular use of paracetamol influences asthma severity, as suggested by the progressively stronger association noted with paracetamol use and increasingly severe asthma in the UK case-control study [33]. Such a study could compare the effect of paracetamol with placebo in adults with mild asthma, with assessment of bronchial hyperresponsiveness as a sensitive physiological marker of asthma and the fraction of exhaled nitric oxide as a measure of eosinophilic airways' inflammation. It would also be possible to investigate the underlying mechanisms of any effect that was demonstrated in such a study.

Conclusion

In conclusion, there is now substantive evidence that the risk of asthma may be increased by exposure to paracetamol in the intrauterine environment, in infancy, later childhood and in adult life. This evidence, as summarized in Table 4, suggests that exposure to paracetamol, incorporating both prescription and over-the-counter use, may represent an important risk factor for the development of asthma. Further research is urgently required, in particular RCTs into the long-term effects of frequent paracetamol use in childhood, to determine the magnitude and characteristics of any such risk. Importantly, RCTs will also enable evidence-based guidelines for the recommended use of paracetamol to be made.

Table 4. The association between paracetamol use and asthma*

Strength of effect	Increased asthma risk: up to 2.1 for paracetamol exposure <i>in utero</i> , 1.5–3.2 for paracetamol use in infancy or childhood, and up to 2.9 for adults
Dose–response	Present for paracetamol exposure <i>in utero</i> , childhood and adult life
Consistency/coherence	Consistency between different studies in different age groups in different populations world-wide
Exposure before response	Observed in studies of paracetamol exposure in the intrauterine environment, in infancy and adult life
Biological plausibility	Through increased oxidant-induced inflammation and potentially enhanced Th2 response
Removal of exposure prevents disease	Not yet examined
Specificity	No increased risk of asthma associated with aspirin or other NSAIDs
Temporal association	International trends of increasing paracetamol use and increasing prevalence of asthma
Analogy	Weak, protective effects of antioxidant diet in asthma

*Evidence presented in accordance with the Bradford Hill criteria [73]. NSAIDs, non-steroidal anti-inflammatory drugs; Th2, T-helper type 2.

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