

Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme



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Summary

Background Exposure to paracetamol during intrauterine life, childhood, and adult life may increase the risk of developing asthma. We studied 6–7-year-old children from Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC) programme to investigate the association between paracetamol consumption and asthma.

Methods As part of Phase Three of ISAAC, parents or guardians of children aged 6–7 years completed written questionnaires about symptoms of asthma, rhinoconjunctivitis, and eczema, and several risk factors, including the use of paracetamol for fever in the child's first year of life and the frequency of paracetamol use in the past 12 months. The primary outcome variable was the odds ratio (OR) of asthma symptoms in these children associated with the use of paracetamol for fever in the first year of life, as calculated by logistic regression.

Findings 205 487 children aged 6–7 years from 73 centres in 31 countries were included in the analysis. In the multivariate analyses, use of paracetamol for fever in the first year of life was associated with an increased risk of asthma symptoms when aged 6–7 years (OR 1.46 [95% CI 1.36–1.56]). Current use of paracetamol was associated with a dose-dependent increased risk of asthma symptoms (1.61 [1.46–1.77] and 3.23 [2.91–3.60] for medium and high use vs no use, respectively). Use of paracetamol was similarly associated with the risk of severe asthma symptoms, with population-attributable risks between 22% and 38%. Paracetamol use, both in the first year of life and in children aged 6–7 years, was also associated with an increased risk of symptoms of rhinoconjunctivitis and eczema.

Interpretation Use of paracetamol in the first year of life and in later childhood, is associated with risk of asthma, rhinoconjunctivitis, and eczema at age 6 to 7 years. We suggest that exposure to paracetamol might be a risk factor for the development of asthma in childhood.

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Introduction

Despite major research efforts, the importance of the many possible risk factors in the development of asthma remains uncertain.^{1–3} The reasons for the increased prevalence of asthma over the past 50 years and the worldwide distribution of its prevalence are poorly understood and are not explained by present knowledge of this disorder. Therefore, the function of novel risk factors that might predispose to the development of asthma has been investigated.

One risk factor that might have a role in the pathogenesis of asthma is the use of paracetamol.^{4,5} Indeed, the risk of asthma may be increased by exposure to paracetamol in the intrauterine environment,^{6–10} infancy,^{7,8,11–13} late childhood,^{12–15} and adult life.^{16–19} These associations have been seen in communities from both developed and developing countries with widely different lifestyles, and do not

seem to be explained by avoidance of aspirin in individuals with asthma. A randomised controlled trial²⁰ showed that in children with asthma paracetamol use for febrile illness was associated with a two-fold higher risk of a hospital outpatient visit for asthma than was ibuprofen.

The increased use of paracetamol over the past 50 years has occurred contemporaneously with the rise in prevalence of asthma worldwide.¹² Paracetamol was marketed internationally in the 1950s as an analgesic replacement for phenacetin,²¹ which was avoided because of nephrotoxic effects. Sales of paracetamol for use in children increased so much that, by 1980, they matched those of aspirin in the USA.^{22,23} By 1985, paracetamol had almost completely replaced aspirin as the analgesic and antipyretic of choice in infants because of concerns about the risk of Reye's syndrome with aspirin use.^{22,23} By 1990, paracetamol had become the most common medication

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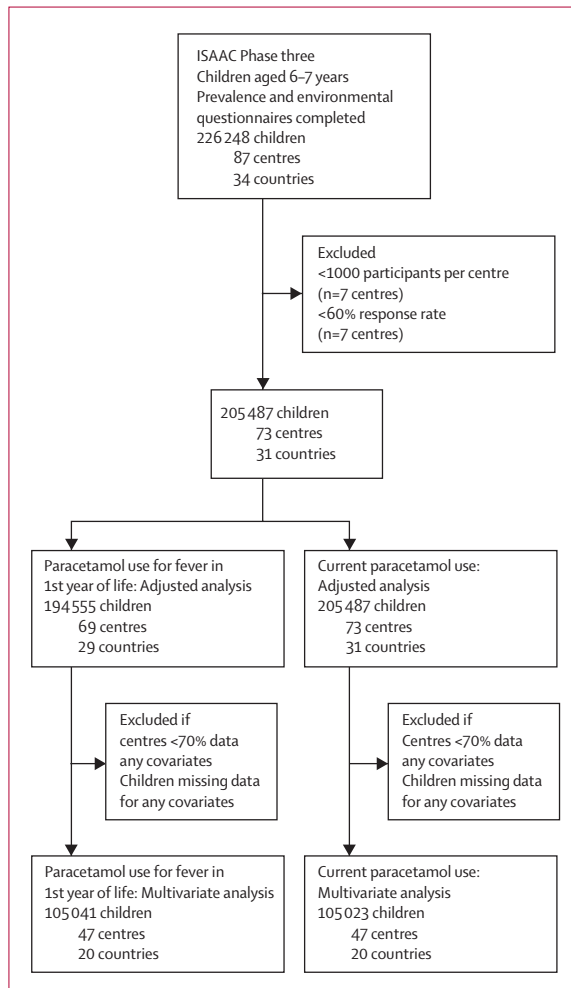


Figure 1: Flow diagram

For the complete questionnaire see <http://isaac.auckland.ac.nz>

in the USA, representing 5% of all treatments dispensed.²⁴

Ecological analyses based on data from countries participating in the International Study of Asthma and Allergies in Childhood (ISAAC) Phase One and the European Community Respiratory Health Survey (ECRHS)²⁵ have identified positive associations between consumption of paracetamol per person and prevalence of asthma in children and adults, respectively. Several biological mechanisms have been proposed to explain the association between paracetamol consumption and asthma,^{4,5,23,26} including development of oxidant-induced airway inflammation due to reduced concentrations of the antioxidant glutathione in the lung and stimulation of the T-helper-cell-2 response, which increases the phenotypic expression of allergic disease.

To investigate this hypothesis, we have analysed the association between paracetamol use and parent-reported symptoms of asthma in 6–7-year-old children from Phase Three of the ISAAC programme.²⁷ We also aimed to explore the consistency of the association between

paracetamol use and asthma by examining the associations with symptoms of rhinoconjunctivitis and eczema.

Methods

Procedures

ISAAC Phase Three is a multicentre, cross-sectional study of two age groups of schoolchildren (6–7-year-old children and 13–14-year-old adolescents) chosen from a random sample of schools in defined geographical areas.^{27,28} Data for exposure to paracetamol in the children in the younger age group are presented in this report. The study consisted of two simple standardised questionnaires that were completed by the parent or guardian of the child.

The first (prevalence) questionnaire, which was about symptoms of asthma, rhinoconjunctivitis, and eczema, was identical to that used in Phase One of the ISAAC programme.^{29–32} The second (environmental) questionnaire was about possible protective and risk factors for the development of asthma and allergic disorders. Questions were about age, sex, family size, birth order, antibiotic use in the first year of life, breastfeeding, birthweight, diet, heating and cooking fuels, exercise, pets, socioeconomic status, immigration status, parental tobacco smoke, traffic pollution, and paracetamol use in the first year of life and in the past 12 months of children aged 6–7 years. Questionnaires were translated into the local language with back-translation into English.

Questions related to paracetamol and terminology used for the responses were: “In the first 12 months of your child’s life, did you usually give paracetamol (eg, Panadol, Pamol) for fever?” “Yes” or “No”. A positive response was referred to as reported use of paracetamol for fever in the first year of life. “In the past 12 months, how often on average have you given your child paracetamol (eg, Panadol, Pamol)?” “Never”, “At least once a year”, or “At least once per month”. A positive response to one of these categories was referred to as no, medium, and high reported current use of paracetamol, respectively. For paracetamol use during the past 12 months, we compared children who took paracetamol once per year or more (medium) and once per month or more (high) with children who never took paracetamol (baseline), to assess the existence of a crude exposure–response relationship.

Symptoms of wheeze were identified by a positive answer to the question: “Has your child had wheezing or whistling in the chest in the past 12 months?” Symptoms of rhinoconjunctivitis were identified by positive answers to the following questions: “In the past 12 months has your child had a problem with sneezing, or a runny or blocked nose when she/he did not have a cold or the flu?” If yes: “In the past 12 months has this nose problem been accompanied by itchy watery eyes?” Symptoms of eczema were identified by positive answers to the following questions: “Has your child ever had an itchy skin rash, which was coming and going for at least 6 months?” If

yes: “Has your child had this itchy rash at any time in the past 12 months?” If yes: “Has this itchy rash at any time affected any of the following places—the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?”

Severe asthma symptoms were identified by one or more answers to the questions: “How many attacks of wheezing has your child had in the past 12 months?” Responses of four or more indicated symptoms of severe asthma; or “In the past 12 months, how often, on average, has your child’s sleep been disturbed due to wheezing?” A response of one or more nights per week indicated symptoms of severe asthma; or “In the past 12 months, has wheezing ever been severe enough to limit your child’s speech to only one or two words at a time between breaths?” A positive response indicated symptoms of severe asthma.

Statistical analysis

To be included in the analysis, centres had to assess at least 1000 children and have a response rate of more than 60%.²⁷ Odds ratios (ORs) were calculated with generalised linear mixed models, with a binomial distribution and logit link, and with the centres being modelled as a random effect. Analyses of all study participants were adjusted for sex, region of the world (Africa, Asia Pacific, Eastern Mediterranean, Latin America, North America, northern and eastern Europe, Oceania, Indian subcontinent, and western Europe), language (Arabic, Chinese, English, Hindi, Indonesian, Portuguese, Spanish and others [ie, many less frequently used languages]), and gross national income (low, lower-middle, upper-middle, and high, as categorised by the World Bank).²⁷ Socioeconomic status of each centre was based on its country’s gross national income. Regression models incorporated the effect of sampling by schools, scaling the size of the sample by the design effect. All analyses were done separately for paracetamol use in the first year of life and at 6–7 years of age.

Multivariate analyses investigated whether the association between symptoms and paracetamol use were confounded by other variables in the environmental questionnaire. For inclusion in these analyses, centres had to have at least 70% of data available for all covariates. In multivariate analyses, children who had a missing value for any of the covariates were removed. Covariates in the multivariate analyses were maternal education (none, primary, secondary, or tertiary), antibiotic use in the first year of life (yes or no), ever breastfed (yes or no), parental smoking (maternal yes or no; paternal yes or no), current diet (three or more fruits per week, one or two per week, or less; three or more vegetables per week, one or two per week, or less; three or more pulses per week, one or two per week, or less), and siblings (younger yes or no; older yes or no).

The primary outcome measure was the association between paracetamol use for fever in the first year of life

	Adjusted* (all children) N=194 555	Adjusted† (children with complete covariate data) N=105 041	Multivariate analysis‡ (children with complete covariate data) N=105 041
Asthma	1.76 (1.68–1.85)	1.77 (1.66–1.89)	1.46 (1.36–1.56)
Rhinoconjunctivitis	1.78 (1.69–1.86)	1.74 (1.62–1.87)	1.48 (1.38–1.60)
Eczema	1.54 (1.47–1.61)	1.54 (1.44–1.64)	1.35 (1.26–1.45)

Data are OR (95% CI). *Adjusted for sex, region of the world, language, and gross national income. A total of 194 555 children were included from 69 centres in 29 countries, except in the analysis of eczema (191 915 children from 68 centres in 28 countries). †Adjusted for sex, region of the world, language, and gross national income. ‡Multivariate analysis included centres with at least 70% data available for all covariates. Children who had a missing value for any of the covariates were removed.

Table 1: Association between paracetamol use for fever in the first year of life and symptoms of asthma, rhinoconjunctivitis, and eczema at 6–7 years of age

	Countries (centres)	Children	OR (95% CI)*		
			Asthma	Rhinoconjunctivitis	Eczema
Africa	1 (1)	917	1.60 (0.20–12.57)	0.70 (0.06–8.74)	0.89 (0.23–3.42)
Asia-Pacific	2 (4)	10 217	1.82 (1.39–2.37)	1.37 (1.09–1.74)	1.45 (1.19–1.76)
Eastern Mediterranean	2 (4)	8 489	1.66 (1.13–2.44)	1.47 (0.86–2.54)	1.11 (0.62–2.00)
Latin America	5 (6)	12 869	1.46 (1.25–1.72)	1.44 (1.22–1.71)	1.49 (1.26–1.76)
North America	2 (2)	2 719	1.25 (0.95–1.64)	1.97 (1.25–3.08)	1.07 (0.75–1.53)
Northern and eastern Europe	3 (3)	6 565	1.29 (1.03–1.61)	1.20 (0.89–1.60)	1.19 (0.94–1.51)
Oceania	1 (4)	9 334	1.79 (1.45–2.21)	2.00 (1.52–2.65)	1.45 (1.17–1.80)
Indian subcontinent	1 (11)	27 411	1.22 (0.96–1.54)	1.71 (1.37–2.15)	1.54 (1.18–2.01)
Western Europe	3 (12)	26 520	1.44 (1.29–1.61)	1.41 (1.25–1.60)	1.30 (1.15–1.46)

Data are numbers. *Multivariate analysis included centres with at least 70% data available for all covariates. Children who had a missing value for any of the covariates were removed. 105 041 children were included from 47 centres in 20 countries.

Table 2: Association between paracetamol use for fever in the first year of life and symptoms of asthma, rhinoconjunctivitis, and eczema at 6–7 years of age worldwide

and asthma symptoms at 6–7 years of age, expressed as OR, as measured by the multivariate analysis.

We did extensive multivariate analyses with multiple imputation on some paracetamol data and other ISAAC environmental-questionnaire exposure data. We showed that little or no bias was introduced by limiting the multivariate analyses to children with complete covariate data. Therefore, we do not show results of additional multivariate analyses with multiple imputation. In sensitivity analyses, we adjusted the association between paracetamol use for fever in the first year of life and symptoms of asthma later in childhood for paracetamol use in the past 12 months; we also adjusted the association between paracetamol use in the past 12 months and current symptoms of asthma for paracetamol use in the first year of life. We also did conditional analyses, in which we calculated the ORs for risk of rhinoconjunctivitis or eczema, associated with paracetamol use, in those who did not respond positively to the question about wheeze in the past 12 months.

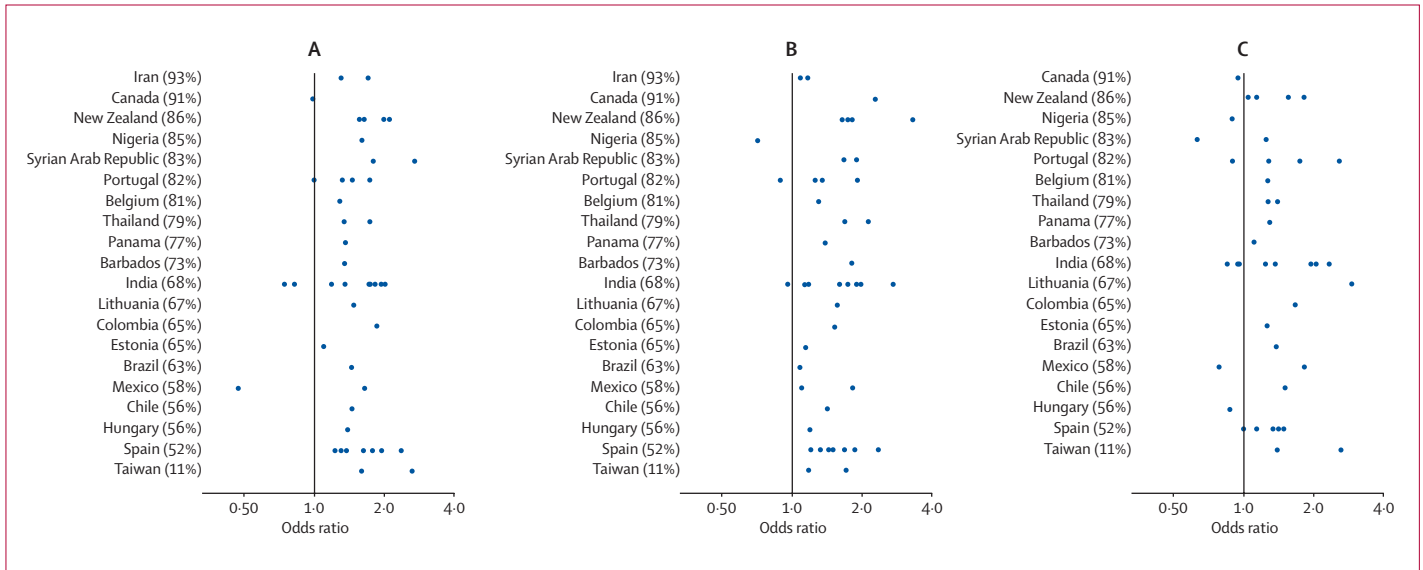


Figure 2: ORs calculated by multivariate analysis for the association between the reported use of paracetamol for fever in the first year of life and symptoms of asthma (A), rhinoconjunctivitis (B) and eczema (C) in children aged 6–7 years
 Children aged 6–7 years old were included from 47 centres in 20 countries. For every country, the percentage of children exposed to paracetamol is stated in brackets.

The population-attributable risk of current asthma symptoms for both paracetamol-use measures was calculated with the Mantel–Haenszel approach, with the adjusted relative risk and the proportion of participants who were exposed. This calculation method makes the assumption of homogeneity.³³ All participating centres obtained local ethics approval. Either passive or active written informed consent was obtained from the parents or guardians, depending on local ethics requirements.

Role of the funding source

The study sponsors had no role in study design; data collection, analysis, data interpretation, writing of the

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report, or in the decision to submit the paper for publication. The authors had the responsibility to write and submit the manuscript for publication, with the involvement of the ISAAC Phase Three Steering Group.

Results

226 248 children aged 6–7 years from 87 centres in 34 countries participated in Phase Three of the ISAAC programme, completing both the prevalence and the environmental questionnaire. After exclusion of seven centres that obtained data for less than 1000 participants, and seven centres that had a response rate lower than 60%, 205 487 children from 73 centres in 31 countries were included in the analysis (figure 1). Exposure and prevalence values by centre are shown in webtable 1, the unadjusted ORs in webtable 2, and the multivariate ORs in webtable 3.

194 555 children aged 6–7 years from 69 centres in 29 countries were included in the analyses of paracetamol use for fever during the first year of life. In these children, the reported use of paracetamol was associated with a significantly increased risk of asthma symptoms (table 1). The risk was similar in all children and in those with complete covariate data (table 1). The increased risk of current asthma symptoms associated with paracetamol use for fever in the first year of life was similar for female and male children (OR 1.79 [95% CI 1.67–1.92] and OR 1.74 [95% CI 1.63–1.85], respectively).

105 041 children aged 6–7 years from 47 centres in 20 countries with complete covariate data were included in the multivariate analyses. In these children, the reported use of paracetamol for fever in the first year of life was

	Adjusted* (all children)	Adjusted† (children with complete covariate data)	Multivariate analysis‡ (children with complete covariate data)
Paracetamol use for fever in first year	1.82 (1.70–1.95)	1.82 (1.65–2.00)	1.43 (1.30–1.58)
Current paracetamol use§			
Medium vs none	1.31 (1.19–1.44)	1.44 (1.26–1.66)	1.33 (1.15–1.53)
High vs none	3.92 (3.56–4.32)	4.23 (3.65–4.91)	3.54 (3.05–4.11)

Data are OR (95% CI). *Adjusted for sex, region of the world, language, and gross national income. For analysis of paracetamol use for fever in first year of life, 192 391 children were included from 68 countries in 29 countries. For analysis of current paracetamol use, 203 361 children were included from 72 centres in 31 countries. †Adjusted for sex, region of the world, language, and gross national income. Analysis was restricted to the centres included in the multivariate analyses. ‡Multivariate analysis included centres with at least 70% data available for all covariates. Children who had a missing value for any of the covariates were removed. For analysis of paracetamol use for fever in the first year of life, 103 284 children were included from 46 centres in 20 countries. For analysis of current paracetamol use, 103 268 children were included from 46 centres in 20 countries. §Paracetamol use was referred as high if it happened once or more per month in the past 12 months; medium if it happened once or more in the past 12 months; and none if it never happened in the past 12 months. Severe asthma symptoms were: sleep disturbed by wheezing one or more nights per week; wheezing severe enough to limit speech; or four or more attacks of wheezing in the past 12 months.

Table 3: Association between paracetamol use and severe asthma symptoms in children aged 6–7 years

associated with a significantly increased risk of current asthma symptoms (table 1). The risk of asthma symptoms was increased in different countries worldwide (p value for homogeneity between regions <0.005) (table 2 and figure 2). For 47 centres combined, the population-attributable risk for asthma symptoms due to paracetamol use for fever in the first year of life was 21%. When current paracetamol use was included in the model, the OR for current asthma symptoms due to paracetamol use for fever in the first year of life was 1.26 (95% CI 1.18–1.36).

The reported use of paracetamol for fever in the first year of life was associated with a significantly increased risk of severe asthma symptoms (table 3). The increase in the risk for severe asthma symptoms was similar to that for current wheeze (tables 1 and 3). For the 47 centres combined, the population-attributable risk for severe asthma symptoms due to paracetamol use for fever in the first year of life was 22%.

The reported use of paracetamol for fever in the first year of life was associated with a significantly increased risk of symptoms of rhinoconjunctivitis and eczema at 6–7 years of age (table 1). The risk was similar in female and male children (data not shown), and was present

in populations with different prevalence of rhinoconjunctivitis and eczema symptoms (table 2 and figure 2). Based on multivariate analyses, population-attributable risks for symptoms of rhinoconjunctivitis and eczema of children aged 6–7 years associated with paracetamol use in the first year of life were 22% and 17%, respectively. When children with wheeze were excluded from the multivariate analysis, the reported use of paracetamol for fever in the first year of life was associated with a significantly increased risk of symptoms of rhinoconjunctivitis and eczema (1.33 [1.18–1.49] and 1.30 [1.18–1.42], respectively).

205 487 children aged 6–7 years from 73 centres in 31 countries were included in the analyses of present use of paracetamol. In these children, the reported use was associated with a significant dose-dependent increased risk of asthma symptoms (table 4). The risk in all children was similar to that in children with complete covariate data (table 4). 105 023 children aged 6–7 years from 47 centres in 20 countries with complete covariate data were included in the multivariate analyses. In these children, the reported use of paracetamol was associated with a significant dose-

	Adjusted† (all children) N=205 487		Adjusted‡ (children with complete covariate data) N=105 023		Multivariate analysis§ (children with complete covariate data) N=105 023	
	Medium vs none	High vs none	Medium vs none	High vs none	Medium vs none	High vs none
Asthma	1.55 (1.46–1.65)	3.45 (3.22–3.69)	1.74 (1.58–1.91)	3.73 (3.35–4.14)	1.61 (1.46–1.77)	3.23 (2.91–3.60)
Rhinoconjunctivitis	1.37 (1.28–1.45)	2.85 (2.65–3.06)	1.42 (1.29–1.56)	3.11 (2.79–3.47)	1.32 (1.20–1.46)	2.81 (2.52–3.14)
Eczema	1.26 (1.18–1.33)	1.94 (1.81–2.07)	1.25 (1.14–1.37)	2.05 (1.85–2.28)	1.18 (1.08–1.30)	1.87 (1.68–2.08)

Data are OR (95% CI). *Paracetamol use was referred as high if it happened once or more per month in the past 12 months; medium if it happened once or more in the past 12 months; and none if it never happened in the past 12 months. †Adjusted for sex, region of the world, language, and gross national income. 205 487 children were included from 73 centres in 31 countries, except for the analysis of eczema (202 702 children from 72 centres in 30 countries). ‡Adjusted for sex, region of the world, language, and gross national income. §Multivariate analysis included centres with at least 70% data available for all covariates. Children who had a missing value for any of the covariates were removed.

Table 4: Association between paracetamol use in the past 12 months and symptoms of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years*

	Countries (centres)	Children	OR (95% CI)†					
			Asthma		Rhinoconjunctivitis		Eczema	
			Medium vs none	High vs none	Medium vs none	High vs none	Medium vs none	High vs none
Africa	1 (1)	895	2.38 (0.06–91)	3.99 (0.12–128)	0.20 (0.01–5.80)	0.47 (0.04–5.97)	0.43 (0.05–3.82)	1.33 (0.22–7.97)
Asia-Pacific	2 (4)	10 188	1.56 (1.14–2.13)	2.87 (1.97–4.20)	1.45 (1.15–1.82)	2.20 (1.56–3.11)	1.34 (1.06–1.70)	2.02 (1.54–2.64)
Eastern Mediterranean	2 (4)	8297	1.37 (0.88–2.11)	2.23 (1.44–3.44)	1.01 (0.60–1.70)	1.50 (0.89–2.55)	1.29 (0.68–2.46)	1.38 (0.71–2.71)
Latin America	5 (6)	12 845	1.50 (1.11–2.02)	2.47 (1.81–3.37)	1.29 (0.95–1.74)	2.48 (1.81–3.39)	1.28 (0.93–1.75)	1.84 (1.33–2.54)
North America	2 (2)	2996	1.19 (0.82–1.71)	2.57 (1.76–3.75)	1.70 (0.90–3.19)	3.85 (2.01–7.35)	1.16 (0.73–1.85)	1.62 (0.99–2.65)
Northern and eastern Europe	3 (3)	6599	1.50 (1.14–1.97)	3.78 (2.55–5.62)	1.29 (0.92–1.82)	2.79 (1.67–4.67)	1.28 (0.97–1.71)	1.99 (1.20–3.30)
Oceania	1 (4)	9240	2.05 (1.51–2.78)	4.34 (3.17–5.96)	1.87 (1.28–2.73)	3.58 (2.42–5.29)	1.28 (0.97–1.69)	1.98 (1.47–2.65)
Indian subcontinent	1 (11)	27 394	1.36 (1.03–1.79)	2.60 (1.90–3.57)	0.98 (0.77–1.24)	2.71 (2.08–3.54)	1.05 (0.78–1.42)	2.41 (1.72–3.37)
Western Europe	3 (12)	26 569	1.83 (1.54–2.18)	4.43 (3.62–5.41)	1.41 (1.18–1.68)	3.57 (2.90–4.40)	1.07 (0.92–1.24)	1.92 (1.58–2.32)

Data are numbers. *Paracetamol use was referred as high if it happened once or more per month in the past 12 months; medium if it happened once or more in the past 12 months; and none if it never happened in the past 12 months. †Multivariate analysis included centres with at least 70% data available for all covariates. Children who have a missing value for any of the covariates were removed.

Table 5: Association between paracetamol use in the past 12 months and symptoms of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years worldwide*

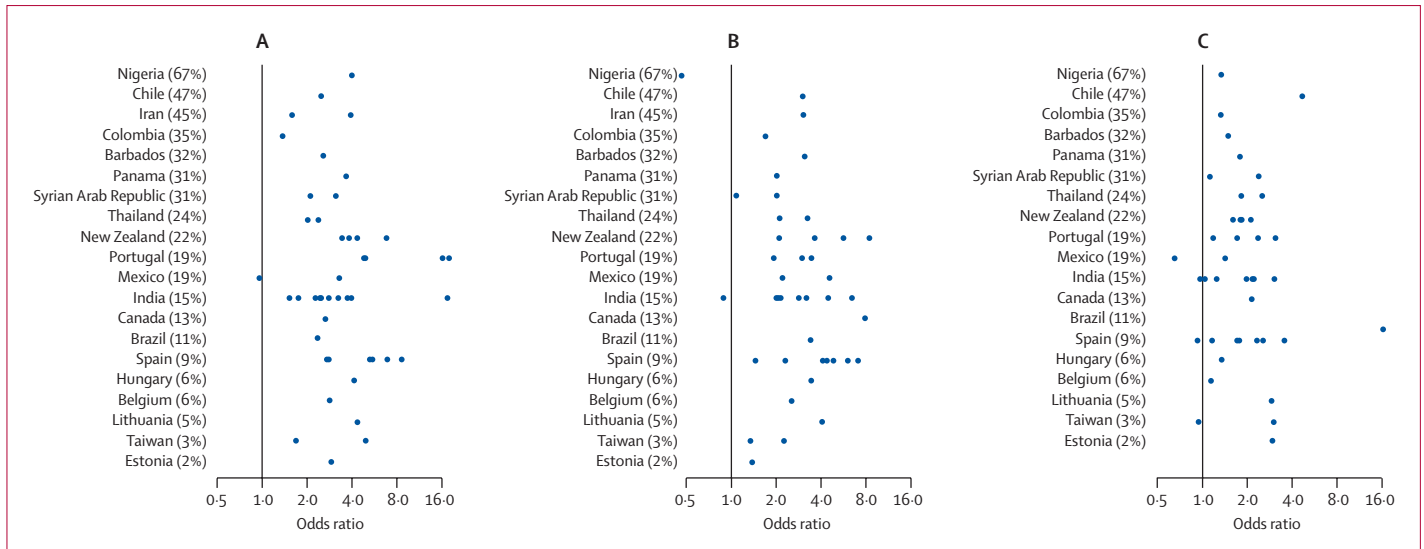


Figure 3: ORs calculated by multivariate analysis for the association between the reported use of paracetamol in the past 12 months (at least once a month vs none) and symptoms of asthma (A), rhinoconjunctivitis (B), and eczema (C) in children aged 6–7 years. Children 6–7 years old were included from 47 centres in 20 countries. For every country, the percentage of children reporting use of paracetamol at least once a month is stated in brackets.

dependent increased risk of asthma symptoms (table 4). The dose-dependent risk was similar for female and male children (data not shown), and was present worldwide (table 5 and figure 3). For the 47 centres combined, the population-attributable risk for asthma symptoms associated with paracetamol use was 40%.

When data from all centres were pooled, 86% of children who were taking paracetamol at least once per month were reported to have used this drug for fever in the first year of life, 68% of those who were taking paracetamol less than once per month, to have used it for fever in the first year of life, and 34% of those who were not taking paracetamol currently to have used it for fever in the first year of their life. When paracetamol use for fever in the first year of life was included in the model, ORs for current asthma symptoms for medium and high paracetamol use versus no use were 1.52 (1.38–1.68) and 3.01 (2.70–3.36), respectively.

The reported use of paracetamol was associated with a significant dose-dependent increased risk of severe asthma symptoms in these children (table 3). Increased risk of severe asthma symptoms was similar to that of current wheeze (tables 3 and 4). For the analysis of the 47 centres combined, the population-attributable risk for severe asthma symptoms due to current paracetamol use was 38%.

The reported use of paracetamol in the past 12 months was associated with a significant dose-dependent increased risk of symptoms of rhinoconjunctivitis and eczema in these children (table 4). The risk was similar for female and male children (data not shown), and was seen worldwide (table 5 and figure 3). For the analysis of the 47 centres combined, the population-attributable risk

for current symptoms of rhinoconjunctivitis and eczema, associated with current paracetamol use were 32% and 20%, respectively.

When children with wheeze were excluded from the multivariate analysis, the reported use of paracetamol was associated with a significantly increased risk of current symptoms of rhinoconjunctivitis (1.20 [1.05–1.38] and 2.13 [1.79–2.53] for medium and high paracetamol use, respectively), and an increased risk of current symptoms of eczema (1.07 [0.95–1.19] and 1.63 [1.42–1.87] for medium and high paracetamol use, respectively).

Discussion

We showed that use of paracetamol for fever in the first year of life is associated with symptoms of asthma later in childhood worldwide. We also recorded a strong dose-dependent association between use of paracetamol and symptoms of asthma in children aged 6–7 years, with a three-fold increased risk associated with frequent paracetamol use, at least once per month. Similarly, we identified associations between use of paracetamol, both in the first year of life and later in childhood, and the risk of severe asthma symptoms, with population-attributable risks of 22% and 38%, respectively. Similar findings were obtained with symptoms of rhinoconjunctivitis and eczema in childhood.

The strengths of the study were its power, size, and multinational nature. As a result, we could establish whether the risk of developing asthma existed in various populations with different asthma prevalence, frequency, and nature of childhood febrile disorders, and different medical practices and health behaviours, environments, and lifestyles.

However, several methodological issues need to be considered in the interpretation of our findings. Questionnaires were completed by the parents or guardians of the children, and information about environmental exposures, such as paracetamol use for fever in the first year of life, was obtained retrospectively, which might have led to recall bias. However, this bias would have contributed to an increased risk associated with paracetamol use only if recall of paracetamol use would have been more accurate in parents of children with asthma than in those of children without asthma. Little evidence exists to support this argument. Most probably, poor recall by all parents would have contributed to reduced ability to measure any effect of paracetamol use.

We gave no emphasis to questions related to paracetamol, which were only two of 28 included in the Phase Three environmental questionnaire. Additionally, the hypothesis that paracetamol used in infancy might predispose to asthma later in childhood is not widely known to the general public or medical staff. Therefore, that parents would have overestimated their child's use of paracetamol for this reason is unlikely. Recognition of symptoms of asthma, rhinoconjunctivitis, and eczema in children was based on validated symptom-based written questionnaires.^{27,28} Symptoms for severe asthma that were used to identify children with clinically significant asthma are positively correlated with national asthma mortality rates.³⁴ We used parent-reported symptoms rather than doctors' diagnoses to avoid major diagnostic differences related to access to medical care, language, and medical practice in populations worldwide.

Further sources of bias might arise from translations of the questionnaires into different languages, and inconsistency across the world in the brand names used for paracetamol. To keep any translation bias to a minimum, investigators followed a standardised protocol, which included back-translation into English.²⁷ Investigators were instructed to substitute locally appropriate brand names in the paracetamol questions to ensure that questions were relevant for the local population. Language was also included in the logistic regression models. Consistency of associations across regions suggests that these potential sources of bias were not important. Selection bias also seems unlikely because the average response rate from centres included in this analysis was 85%.

Another important issue is whether the association might have been confounded by other factors that determine the risk of developing childhood asthma or use of paracetamol. To address this issue, we adjusted ORs for factors such as region of the world and gross national income, and we did multivariate analyses in which other potential confounding variables were controlled for. Factors such as antibiotic use in the first year of life and maternal educational status were taken into account because they might have been associated with the

prescription or over-the-counter use of paracetamol in infancy. Other factors, such as current diet or maternal smoking were taken into account because they might have worked through similar mechanisms, such as enhancement of oxidative damage. When analyses were adjusted for these potential confounders, the strength of the association between paracetamol use for fever in the first year of life and asthma reduced from 1.76 to 1.46 but remained significant. The reduced association in the multivariate analysis suggests that some confounding factors are likely to have been present and that, if residual confounding exists, the ORs presented may be overestimates of the risk. For current paracetamol use and asthma, the strength of the dose-dependent association persisted in the multivariate analyses. Although multivariate analyses were done only in children with complete covariate data, this subgroup was representative of the full dataset in terms of risk.

The extent to which our findings might have been due to confounding by indication cannot be directly assessed in a study with this cross-sectional design. However, the observation that the association was present worldwide in communities with different types of childhood febrile illnesses, and different medical practices and over-the-counter medication use suggests that confounding by indication might not have been a major factor. Additionally, fever is common in infants, with about 1–2% of infants having documented fever (>38°C) and about 4% having symptoms of fever on any one day.^{35,36} Consequently, most infants would have an indication to receive paracetamol for fever on more than one occasion during their first year of life.

Illnesses of the lower respiratory tract in early life, in particular respiratory syncytial virus infection, are associated with an increased risk of wheezing in children aged 6 years.³⁷ Paracetamol use for such episodes could cause confounding in our study. However, paracetamol is also given worldwide to infants for fever unrelated to illnesses of the lower respiratory tract, encompassing several conditions, including malaria, post-vaccination fever, otitis media, pharyngitis, dengue fever, infectious diarrhoea, urinary tract infection, measles, whooping cough, and fever of no known cause.^{8,15,38–45} The use of paracetamol in the first year of life for such febrile illnesses would not be expected to lead to confounding by indication in our study because these disorders are not associated with an increased risk of childhood asthma. Although paracetamol use in 6–7-year-old-children is unlikely to be affected by indication, it could be affected by reverse causation if children with asthma were more likely to develop febrile episodes and, as a result, have greater paracetamol use than do non-affected children. However, this situation would not explain the association between paracetamol use and eczema, independent of asthma, because symptoms and complications of eczema are not typically associated with use of paracetamol.

The possibility that children with asthma received paracetamol instead of aspirin or other non-steroidal anti-inflammatory drugs to prevent precipitating asthma attacks is not relevant to the use of paracetamol for fever in the first year of life, because aspirin is contraindicated and seldom used in infancy because of the risk of causing Reye's syndrome.^{22,23} However, this possibility is relevant to the use of analgesic and antipyretic agents by children aged 6–7 years with asthma. Aspirin avoidance in children with asthma is uncommon because aspirin sensitivity seldom occurs and may not be recognised in children with asthma.^{46,47}

Parents who gave paracetamol to their infants were more likely to do so later in childhood. However, the risk of use of paracetamol for fever in the first year of life existed independently of current paracetamol use, and vice versa.

Several factors suggest that the association between paracetamol use and asthma may have a cause–effect relationship. First, paracetamol use in infancy and frequent use later in childhood strongly increased the risks of asthma. Second, current paracetamol use showed a strong dose–response relationship. Third, a consistent association between paracetamol use and asthma in populations with different lifestyles and medical practices existed, as it was in other cross-sectional and longitudinal studies in different age groups.^{6–19} Furthermore, in one randomised controlled trial,²⁰ paracetamol use for fever in childhood was associated with an increased risk of hospital outpatient attendance for asthma when compared with ibuprofen. Fourth, similar to the findings of intrauterine exposure to paracetamol, our results suggest that exposure preceded the response. This interpretation is based on the fact that wheezing in the first year of life is often self-limiting and not a reliable predictor of asthma in later childhood.^{48–51} Finally, there is a temporal association between the worldwide trends towards increasing paracetamol use in childhood over the past 50 years^{21–24} and the increase in prevalence of childhood asthma in many countries during this period.^{1,2}

The increased risk of rhinoconjunctivitis and eczema suggests that the effect of paracetamol is not restricted to the airways. This finding is consistent with the main mechanisms that have been proposed to explain the association between paracetamol and risk of asthma and atopic diseases.^{4,5,23,26} Paracetamol use at recommended therapeutic doses could result in depletion of glutathione and glutathione-dependent enzymes, thereby reducing the ability to withstand oxidative stress. The generation of reactive oxygen species after allergic, viral, or other non-allergic stimuli may then result in enhanced inflammation, which could lead to the development or worsening of pre-existing asthma, rhinoconjunctivitis, or eczema, dependent on the organ systems affected. Low glutathione concentrations could affect the expression of T-helper-cell pathways by altering antigen presentation and recognition, thereby favouring the T-helper-cell-2

dominant pathway. One therapeutic dose of paracetamol could reduce total serum anti-oxidant capacity;⁵² therefore, both these proposed mechanisms could be valid for the intermittent use of paracetamol. The off-label use of paracetamol in children is common, with parents and doctors administering doses of paracetamol either higher or lower than those recommended.^{53,54}

Overall, this study provides further worldwide evidence that the use of paracetamol in childhood can increase the risk of developing asthma and related allergic disorders. Although causality cannot be established from a study with this design, we suggest that exposure to paracetamol might be an important putative risk factor for the development of asthma. However, evidence is insufficient to advise parents and health-care workers of the risk–benefit of taking paracetamol in childhood, or its comparative efficacy and safety with other approaches. Further research is urgently needed, including randomised controlled trials, into the long-term effects of paracetamol to enable evidence-based guidelines for the recommended use of paracetamol in childhood to be made.

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Conflict of interest statement

RB received honoraria for lectures and participation in advisory boards, and grant support from GlaxoSmithKline, the manufacturer of paracetamol. All other authors declare that they have no conflict of interest.

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