Acetaminophen Use and Risk of Asthma, Rhinoconjunctivitis, and Eczema in Adolescents

International Study of Asthma and Allergies in Childhood Phase Three

Richard W. Beasley[1], Tadd O. Clayton[2], Julian Crane[3], Christopher K. W. Lai[4], Stephen R. Montefort[5], Erika von Mutius[6], Alistair W. Stewart[2], and the ISAAC Phase Three Study Group*

[1]Medical Research Institute of New Zealand, Wellington, New Zealand,; [2]Faculty of Medical and Health Sciences, The University of Auckland, Auckland;, New Zealand. [3]Otago University Wellington, Wellington, New Zealand; [4]Chinese University of Hong Kong, Hong Kong, SAR China; [5]University of Malta, Malta, and [6]Dr von Haunersches University Children's Hospital, Ludwig-Maximilians-University, Munich, Germany

***Rationale*: There is epidemiological evidence that the use of acetaminophen may increase the risk of developing asthma.**

***Objectives*: To investigate the risk of asthma and other allergic disorders associated with the current use of acetaminophen in 13- to 14-year-old children in different populations worldwide.**

***Methods*: As part of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three, 13- to 14-year-old children completed written and video questionnaires obtaining data on current symptoms of asthma, rhinoconjunctivitis, and eczema, and a written environmental questionnaire obtaining data on putative risk factors, including acetaminophen use in the past 12 months.**

***Measurements and Main Results*: The primary outcome measure was the odds ratio (OR) of current asthma symptoms associated with acetaminophen use calculated by logistic regression. A total of 322,959 adolescent children from 113 centers in 50 countries participated. In the multivariate analyses the recent use of acetaminophen was associated with an exposure-dependent increased risk of current asthma symptoms (OR, 1.43 [95% confidence interval, 1.33–1.53] and 2.51 [95% confidence interval, 2.33–2.70] for medium and high versus no use, respectively). Acetaminophen use was also associated with an exposure-dependent increased risk of current symptoms of rhinoconjunctivitis and eczema.**

***Conclusions*: Acetaminophen use may represent an important risk factor for the development and/or maintenance of asthma, rhinoconjunctivitis, and eczema in adolescent children.**

Keywords: acetaminophen; ISAAC; asthma; rhinoconjunctivitis; eczema

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

There is epidemiological evidence that exposure to acetaminophen in the intrauterine environment, early childhood, and adult life is associated with an increased risk of asthma. The potential mechanisms for these effects of acetaminophen include oxidant-induced airways inflammation and enhanced Th2 responses.

What This Study Adds to the Field

Acetaminophen use may represent an important risk factor for the development and/or maintenance of asthma, rhinoconjunctivitis, and eczema in adolescents.

Evidence is accumulating that the use of acetaminophen may increase the risk of developing asthma and that its widespread increasing use over the last 30 years may have contributed to the increasing prevalence of asthma in different countries worldwide (1, 2). The evidence is based primarily on epidemiological studies, which have reported that exposure to acetaminophen in the intrauterine environment (3–7), childhood (6, 8, 9), and adult life (10–13) is associated with an increased risk of asthma, together with one randomized controlled trial reporting increased rates of hospital visits for asthma in children taking acetaminophen compared with ibuprofen (14). The potential mechanisms for these effects of acetaminophen include oxidant-induced airways inflammation and enhanced Th2 responses (1, 2, 15).

Recently we have observed from Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC) that the reported use of acetaminophen in the first year of life was associated with an increased risk of current asthma symptoms in 6- to 7-year-old children (9). Recent acetaminophen use was also associated with a dose-dependent increased risk of current asthma symptoms in the 6- to 7-year-old children. ISAAC Phase Three also surveyed 13- to 14-year-old children, which provided the opportunity of examining whether the associations between acetaminophen use and asthma in young children extended to adolescent children. In this article we report the findings from these analyses.

METHODS

ISAAC Phase Three is a multicenter, multicountry, cross-sectional study of two age groups of schoolchildren (6- to 7-year-olds and 13- to 14-year-olds) chosen from a random sample of schools in defined geographical areas within each center (16, 17). The data for the 13- to 14-year-old children (referred to in this article as adolescents) are presented in this article. The study instruments were two written questionnaires and a video questionnaire that were completed by the adolescent. The first written questionnaire (prevalence) obtained data

(*Received in original form May 12, 2010; accepted in final form August 13, 2010*)

* A complete list of members may be found before the beginning of the REFERENCES.

The individual centers and collaborators that undertook ISAAC Phase Three were funded by numerous sources throughout the world. Currently, the main source of funding for the ISAAC International Data Centre (IIDC) is The BUPA Foundation. Many New Zealand funding bodies have contributed support for the IIDC during the periods of fieldwork and data compilation (the Health Research Council of New Zealand, the Asthma and Respiratory Foundation of New Zealand, the Child Health Research Foundation, the Hawke's Bay Medical Research Foundation, the Waikato Medical Research Foundation, Glaxo Wellcome New Zealand, the NZ Lottery Board, and Astra Zeneca New Zealand). Glaxo Wellcome International Medical Affairs supported the regional coordination for Phase Three and the IIDC.

Correspondence and requests for reprints should be addressed to Richard W. Beasley, D.Sc., Medical Research Institute of New Zealand, Private Bag 7902, Wellington 6242, New Zealand. E-mail: Richard.Beasley@mrinz.ac.nz

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 183. pp 171–178, 2011
Originally Published in Press as DOI: 10.1164/rccm.201005-0757OC on August 13, 2010
Internet address: www.atsjournals.org

on demographic characteristics and on asthma, rhinoconjunctivitis, and eczema symptoms. The second written questionnaire (environmental) obtained data on a wide range of putative protective and risk factors for the development of asthma and allergic disorders. The written questionnaires were translated into the local language with back-translation into English (18). The video questionnaire showed different audiovisual scenes of clinical asthma. The complete written questionnaires and information concerning the video questionnaire can be found on the ISAAC Web site at http://isaac.auckland.ac.nz.

The question relating to acetaminophen use was:

"In the past 12 months, how often on average have you taken paracetamol (e.g., Panadol, Pamol)?" Never/At least once a year/At least once per month.

Adolescents in the 1+ per year (medium) and 1+ per month (high) categories were compared with those in the "never" category.

A participant was considered to have current asthma symptoms (current wheeze) if they provided a positive response to the written question "Have you had wheezing or whistling in the chest in the past 12 months?"

A participant was considered to have current symptoms of rhinoconjunctivitis if they provided positive responses to both these written questions:

"In the past 12 months have you had a problem with sneezing or a runny or blocked nose when you 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?"

A participant was considered to have current symptoms of eczema if they provided positive responses to both these written questions:

"Have you ever 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?" (These questions were preceded by the question "Have you ever had an itchy skin rash which was coming and going for at least 6 months?").

Symptoms of severe asthma were defined by the responses to the following written questions:

1. "How many attacks of wheezing have you had in the past 12 months"? None/1 to 3/4 to 12/More than 12. Participants who reported four or more attacks were considered to have symptoms of severe asthma.
2. "In the past 12 months how often, on average, has your sleep been disturbed due to wheezing?" Never woken with wheezing/Less than one night per week/One or more nights per week. A response of one or more nights per week was considered to indicate symptoms of severe asthma.
3. "In the past 12 months, has the wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?" Yes/No. A positive response was considered to indicate symptoms of severe asthma.

For the video questionnaire, participants viewed five scenes of clinical asthma and were asked to indicate whether they had experienced similar symptoms "ever," and if yes, "in the past year." A participant was considered to have current wheeze (video) if they provided a positive response "in the past year" to the first scene, showing a person wheezing at rest.

Adherence to the protocol was assessed by the ISAAC International Data Centre and centers with serious discrepancies were excluded.

Analysis

To be included in the analysis, centers were required to have studied at least 1,000 children and have a response rate of greater than 70%. Odds ratios (ORs) were calculated using generalized linear mixed models with a binomial distribution and logit link and with centers being modeled as a random effect. The analyses on all study participants were adjusted for sex, region of the world, language, and gross national income as previously described (9).

Multivariate analyses were conducted to investigate whether the association between symptoms and acetaminophen use were confounded by other variables in the environmental questionnaire. For inclusion in these analyses, centers were required to have at least 70% data available for all covariates; subjects who had a missing value for any of the covariates were removed. The covariates included in the multivariate analyses were maternal education, current maternal smoking, siblings, and current consumption of vegetables and fruit, as previously described (9).

The primary outcome measure was the association between current acetaminophen use and current asthma symptoms, expressed as the OR (medium versus none, high versus none) as determined by multivariate analysis.

Conditional analyses were also undertaken in which the ORs were calculated for the risk of rhinoconjunctivitis or eczema associated with acetaminophen use in those who did not report wheezing in the past 12 months.

The population attributable risk of current symptoms due to each acetaminophen use measure was calculated using the Mantel-Haenszel approach using the adjusted relative risk and the proportion of the participants who were exposed. This calculation method makes the homogeneity assumption (19).

All analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

Ethics Approval

All participating centers obtained local ethics approval.

Role of the Funding Sources

The funders of the study had no role in study design; in the collection, analysis, and interpretation of data; in writing of the report; or in the decision to submit the paper for publication.

RESULTS

There were 361,598 13- to 14-year-old adolescents from 122 centers in 54 countries who completed the Phase Three environmental questionnaire (Figure 1). Nine centers were excluded because they did not include the acetaminophen question or had less than 70% data for current acetaminophen use. Participants with missing data for sex or current acetaminophen use were excluded at this stage. These exclusions resulted

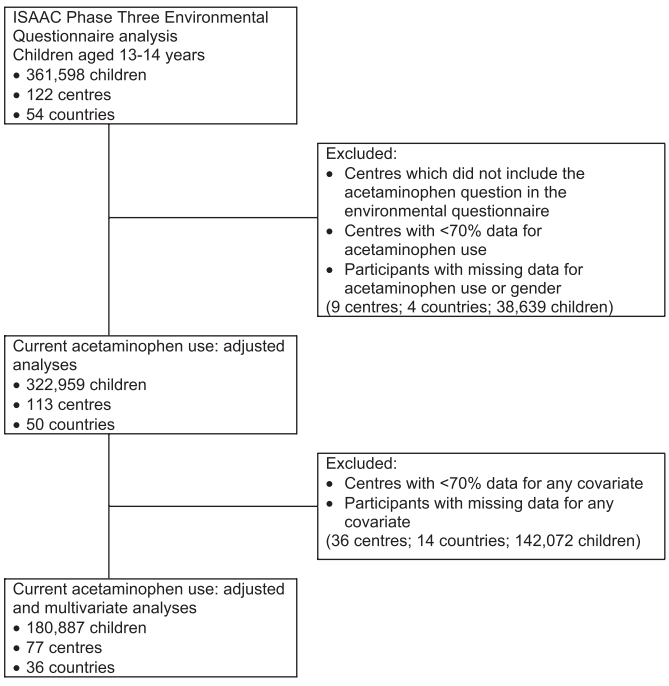

Figure 1. Flow diagram of inclusion of children, centers, and countries. ISAAC = International Study of Asthma and Allergies in Childhood.

in 322,959 adolescents from 113 centers in 50 countries contributing data to the analyses presented. Following the exclusion of centers in which there was less than 70% data for any covariate, and of participants for whom there were missing data for any covariate, there were 180,887 adolescents from 77 centers in 36 countries included in the multivariate analyses.

The mean percentage of children exposed to acetaminophen at least once a month was 30%, with levels ranging from 2% in Taiwan to 68% in Nigeria (Figure 2A). The mean percentage of children exposed to acetaminophen at least once in the previous 12-month period was 73%, ranging from 41% in China to 92% in Panama.

Asthma

The reported use of acetaminophen in the past 12 months was associated with a significant exposure-dependent increased risk of current asthma symptoms (Table 1). In the adjusted analyses, the ORs for current asthma symptoms for medium (1+/y) and high (1+/mo) acetaminophen use compared with no use were 1.38 (95% confidence interval [CI], 1.31–1.46) and 2.36 (95% CI,

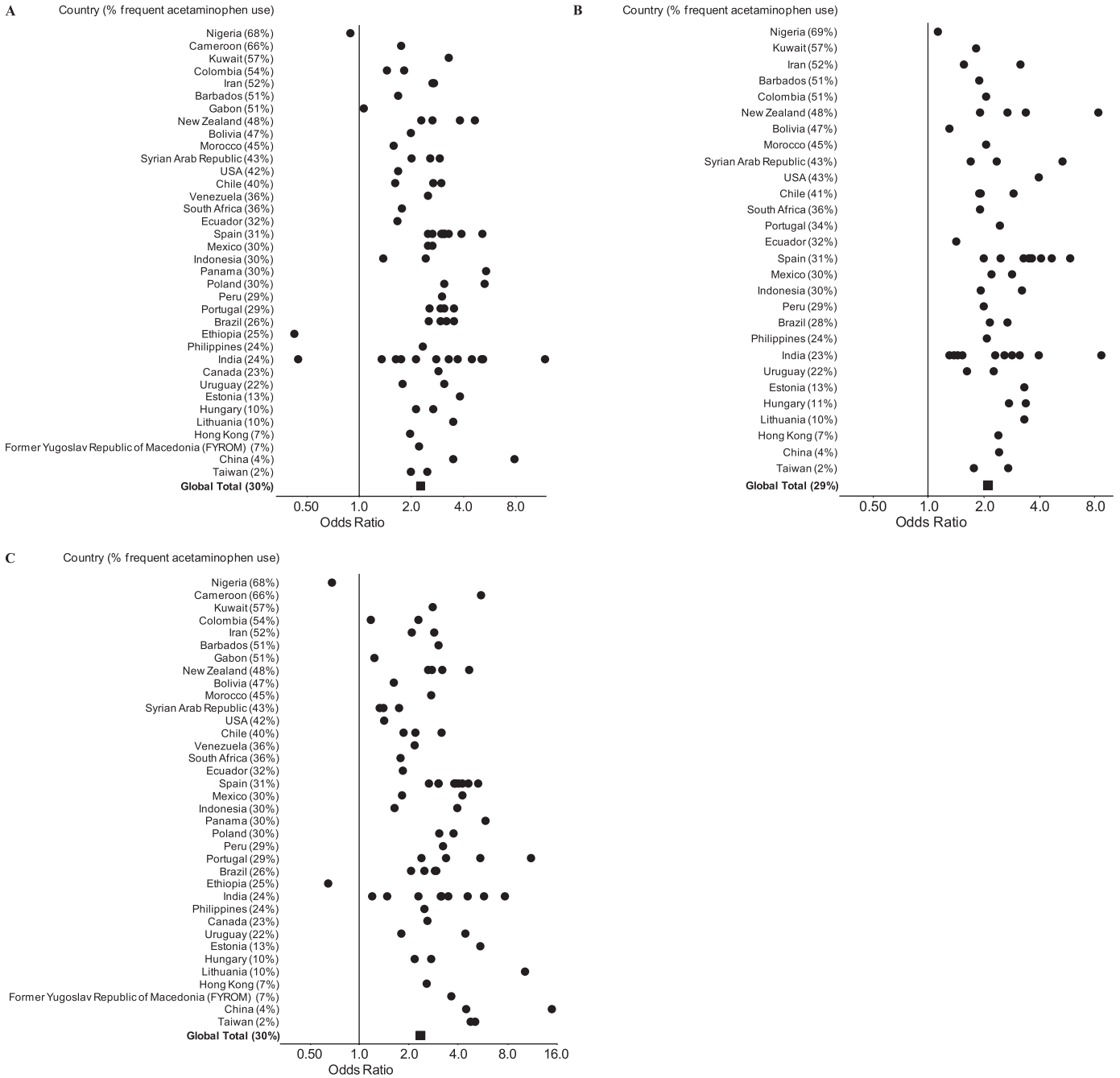

Figure 2. Plot showing the odds ratios for the association between the reported use of acetaminophen in the past 12 months (at least once a month versus none) and (*A*) current wheeze, (*B*) current wheeze (video), and (C) severe asthma symptoms in 13- to 14-year-old children. *Circles* represent the odds ratios for each of the 77 centers in 36 countries; *squares* represents the global odds ratio. For every country, the percentage of children exposed to acetaminophen (at least once a month) is stated in brackets.

TABLE 1. THE ASSOCIATION BETWEEN ACETAMINOPHEN USE IN PAST 12 MONTHS AND ASTHMA SYMPTOMS

		Odds Ratio (95% CI)					
		Adjusted† (All Children)		Adjusted‡ (Children with Complete Covariate Data)		Multivariate Analysis§ (Children with Complete Covariate Data)	
	Number of Participants with Each Symptom*	Medium vs. Never	High vs. Never	Medium vs. Never	High vs. Never	Medium vs. Never	High vs. Never
Current wheeze	35,146	1.38 (1.31–1.46)	2.36 (2.24–2.50)	1.42 (1.34–1.52)	2.47 (2.31–2.64)	1.43 (1.33–1.53)	2.51 (2.33–2.70)
Current wheeze (video)	18,528	1.29 (1.20–1.39)	2.15 (2.00–2.32)	1.33 (1.22–1.45)	2.29 (2.10–2.51)	1.36 (1.24–1.49)	2.35 (2.13–2.60)
Severe asthma	17,199	1.25 (1.17–1.34)	2.50 (2.34–2.68)	1.29 (1.19–1.39)	2.67 (2.47–2.88)	1.33 (1.22–1.45)	2.75 (2.52–3.00)
Asthma ever	37,355	1.23 (1.17–1.28)	1.81 (1.73–1.90)	1.24 (1.18–1.31)	1.87 (1.77–1.98)	1.24 (1.17–1.31)	1.88 (1.77–1.99)

Definition of abbreviation: CI = confidence interval.

Current acetaminophen use: high = 1+/mo in past 12 months; medium = 1+ in past 12 months; never = none in past 12 months. Current wheeze = wheeze in the past 12 months (written questionnaire). Current wheeze (video) = wheeze in the past 12 months (video questionnaire). Severe asthma symptoms = sleep disturbed due to wheezing on average 1 or more nights per week, or wheezing severe enough to limit speech, or four or more attacks of wheezing in the past 12 months.

* Adjusted analysis.

† Adjusted for sex, region of the world, language, and gross national income. A total of 322,959 children were included from 113 centers in 50 countries. For current wheeze (video), a total of 253,280 children were included from 89 centers in 37 countries.

‡ Adjusted for sex, region of the world, language, and gross national income. Analysis restricted to the centers included in the multivariate analyses.

§ Multivariate analysis including centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Covariates included maternal education, maternal smoking, current diet, siblings. A total of 180,887 children were included from 77 centers in 36 countries. For current wheeze (video), a total of 140,059 children were included from 60 centers in 28 countries.

2.24–2.50), respectively. In the multivariate analyses the ORs for current asthma symptoms for medium and high acetaminophen use compared with no use were 1.43 (95% CI, 1.33–1.53) and 2.51 (95% CI, 2.33–2.70), respectively. The exposure-dependent increased risk of current asthma symptoms with acetaminophen use was present throughout the major regions of the world (Table 2, Figure 2). The population attributable risk for asthma symptoms associated with current acetaminophen use was 41%.

The reported current use of acetaminophen was associated with a significant exposure-dependent increased risk of current wheeze (video) (Table 1, Figure 2). The reported current use of acetaminophen was associated with a significantly increased risk of symptoms of severe asthma (Table 1, Figure 2). The magnitude of the increased risks of current wheeze (video) and symptoms of severe asthma were similar to those for current wheeze. The population attributable risk for symptoms of severe asthma due to current acetaminophen use was 43%.

Rhinoconjunctivitis and Eczema

The reported use of acetaminophen in the past 12 months was associated with a significant dose-dependent increased risk of current symptoms of rhinoconjunctivitis and eczema (Table 3). The risk was observed in most regions of the world (Table 4, Figure 3). The population attributable risk for current symptoms of rhinoconjunctivitis and eczema associated with current acetaminophen use was 36% and 40%, respectively.

When participants with current wheeze were excluded from the multivariate analysis, the use of acetaminophen was associated with a significantly increased risk of current symptoms of rhinoconjunctivitis with ORs of 1.33 (95% CI, 1.25–1.42) and 2.18 (95% CI, 2.04–2.33) for medium and high acetaminophen use, respectively. Likewise, when participants with current wheeze were excluded from the analysis, there was an increased risk of current symptoms of eczema associated with the use of acetaminophen with ORs of 1.32 (95% CI, 1.21–1.44) and 1.87 (95% CI, 1.7–2.05) for medium and high acetaminophen use, respectively. Similar estimates of risk were observed when participants with asthma ever were excluded from the multivariate analysis, for both current symptoms of rhinoconjunctivitis and symptoms of eczema (*see* online supplement).

DISCUSSION

This study has identified that the reported use of acetaminophen in 13- to 14-year-old adolescent children was associated with an exposure-dependent increased risk of asthma symptoms. The association was present in all major regions of the

TABLE 2. THE ASSOCIATION BETWEEN ACETAMINOPHEN USE IN THE PAST 12 MONTHS AND CURRENT SYMPTOMS OF ASTHMA IN DIFFERENT REGIONS OF THE WORLD

					Odds Ratio (95% CI)*	
	Countries (No.)	Centers (No.)	Subjects (No.)	Current Wheeze (No.)	Medium vs. Never	High vs. Never
Africa	6	6	12,285	1,635	1.03 (0.74–1.45)	1.20 (0.88–1.65)
Asia-Pacific	5	8	24,405	1,412	1.54 (1.32–1.80)	2.11 (1.65–2.68)
Eastern Mediterranean	3	6	12,970	1,038	1.69 (1.07–2.67)	2.60 (1.68–4.02)
Indian subcontinent	1	12	26,345	1,305	1.20 (0.91–1.58)	2.71 (2.05–3.58)
Latin America	10	18	41,136	6,794	1.36 (1.19–1.55)	2.35 (2.05–2.68)
North America	3	3	5,741	1,007	1.09 (0.78–1.53)	2.12 (1.52–2.96)
Northern and Eastern Europe	5	7	18,860	1,486	1.37 (1.15–1.64)	2.67 (2.16–3.31)
Oceania	1	4	8,796	2,227	2.00 (1.42–2.82)	3.74 (2.67–5.23)
Western Europe	2	13	30,349	3,723	1.74 (1.45–2.08)	3.18 (2.64–3.82)

Definition of abbreviation: CI = confidence interval.

Current acetaminophen use: high = 1+/mo in past 12 months; medium = 1+ in past 12 months; never = none in past 12 months.

* Multivariate analysis included centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Covariates included maternal education, maternal smoking, current diet, siblings. Adjusted for sex, region of the world, language, and gross national income. A total of 180,887 children were included from 77 centers in 36 countries.

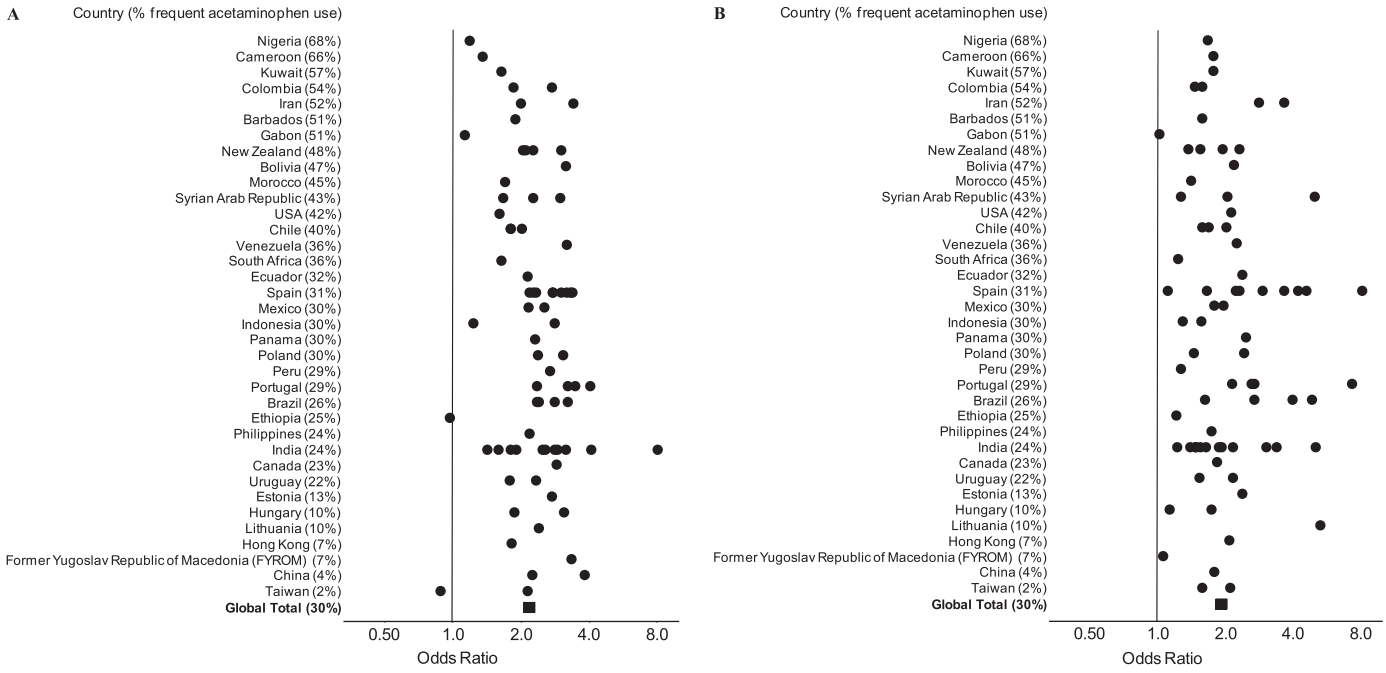

Figure 3. Plot showing the odds ratios for the association between the reported use of acetaminophen in the past 12 months (at least once a month versus none) and current symptoms of (*A*) rhinoconjunctivitis and (*B*) eczema in 13- to 14-year-old children. *Circles* represent the odds ratios for each of the 77 centers in 36 countries; *squares* represents the global odds ratio. For each country, the percentage of children exposed to acetaminophen (at least once a month) is stated in brackets.

world and persisted in the multivariate analyses, which controlled for confounding variables. The magnitude of the association was substantial, with a 2.5-fold increased risk associated with frequent acetaminophen use at least once per month. Similar magnitudes of risk were observed with symptoms of severe asthma determined by written questionnaire and with current wheeze when assessed by video questionnaire, both measures of clinically significant asthma (20–23). The public health significance of the findings is suggested by the population attributable risk for symptoms of severe asthma due to acetaminophen of 43%. Significant associations were also observed between current acetaminophen use and the risk of the related conditions rhinoconjunctivitis and eczema.

These findings extend our previous observations from ISAAC Phase Three, that the use of acetaminophen in infancy and current use was associated with an increased risk of asthma symptoms in 6- to 7-year-old children. Although many of the methodological issues relating to the earlier study also apply to analyses in the 13- to 14-year-old age group, there are also some differences that are relevant to the interpretation of the study findings. First, the current study had greater power and worldwide representation, with around 320,000 adolescents from 113 centers in 50 countries compared with around 200,000 6- to 7-year-old children from 73 centers in 31 countries. Second, we used a video questionnaire in which the audiovisual presentation of clinical asthma in different situations was presented. Validation studies have shown that the video questionnaire has high sensitivity and specificity for identifying children with bronchial hyperresponsiveness, providing data relatively free from bias due to language and culture (20–22).

Confounding by indication represented the most important consideration in the interpretation of the primary 6- to 7-year-

TABLE 3. THE ASSOCIATION BETWEEN ACETAMINOPHEN USE IN THE PAST 12 MONTHS AND CURRENT SYMPTOMS OF RHINOCONJUNCTIVITIS AND ECZEMA

		Odds Ratio (95% CI)					
		Adjusted† (All Children)		Adjusted‡ (Children with Complete Covariate Data)		Multivariate Analysis§ (Children with Complete Covariate Data)	
	Number of Participants with Each Symptom*	Medium vs. Never	High vs. Never	Medium vs. Never	High vs. Never	Medium vs. Never	High vs. Never
Rhinoconjunctivitis	45,017	1.34 (1.28–1.40)	2.23 (2.13–2.35)	1.38 (1.31–1.47)	2.40 (2.26–2.55)	1.38 (1.29–1.47)	2.39(2.24–2.55)
Eczema	22,134	1.28 (1.20–1.36)	1.90 (1.78–2.03)	1.31 (1.22–1.41)	1.97 (1.82–2.12)	1.31 (1.21–1.42)	1.99 (1.82–2.16)

Definition of abbreviation: CI = confidence interval.

Current acetaminophen use: high = 1+/month in past 12 months; medium = 1+ in past 12 months; never = none in past 12 months.

* Adjusted analysis.

† Adjusted for sex, region of the world, language, and gross national income. A total of 322,959 children were included from 113 centers in 50 countries.

‡ Adjusted for sex, region of the world, language, and gross national income. Analysis restricted to the centers included in the multivariate analyses.

§ Multivariate analysis including centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Covariates included maternal education, maternal smoking, current diet, siblings. A total of 180,887 children were included from 77 centers in 36 countries.

TABLE 4. THE DOSE-DEPENDENT ASSOCIATION BETWEEN ACETAMINOPHEN USE IN THE PAST 12 MONTHS AND CURRENT SYMPTOMS OF RHINOCONJUNCTIVITIS AND ECZEMA IN DIFFERENT REGIONS OF THE WORLD

	Rhinoconjunctivitis			Eczema		
		Odds Ratio (95% CI)*			Odds Ratio (95% CI)*	
	Current Rhinoconjunctivitis (No.)	Medium vs. Never	High vs. Never	Current Eczema (No.)	Medium vs. Never	High vs. Never
Africa	2,055	1.30 (1.01–1.67)	1.38 (1.07–1.78)	1,787	1.45 (1.14–1.85)	1.30 (1.01–1.67)
Asia-Pacific	3,096	1.40 (1.23–1.60)	1.95 (1.54–2.45)	881	1.29 (1.07–1.56)	1.57 (1.19–2.06)
Eastern Mediterranean	1,419	1.31 (0.92–1.85)	2.14 (1.55–2.97)	547	1.82 (1.09–3.02)	2.34 (1.44–3.81)
Indian subcontinent	1,987	1.40 (1.12–1.75)	2.29 (1.82–2.89)	793	1.05 (0.80–1.38)	1.78 (1.34–2.38)
Latin America	7,793	1.36 (1.19–1.56)	2.41 (2.11–2.76)	4,425	1.28 (1.07–1.53)	2.09 (1.75–2.49)
North America	877	1.14 (0.84–1.54)	2.17 (1.61–2.92)	438	1.41 (0.90–2.21)	1.95 (1.23–3.09)
Northern and Eastern Europe	1,815	1.50 (1.27–1.76)	2.52 (2.08–3.06)	1,080	1.27 (1.04–1.55)	1.87 (1.47–2.38)
Oceania	1,471	1.15 (0.84–1.59)	2.38 (1.75–3.24)	683	1.26 (0.74–2.16)	1.77 (1.05–3.00)
Western Europe	4,352	1.53 (1.29–1.80)	2.87 (2.42–3.40)	1,378	1.56 (1.25–1.93)	2.67 (2.14–3.33)

Definition of abbreviation: CI = confidence interval.

Current acetaminophen use: high = 1+/mo in past 12 months; medium = 1+ in past 12 months; never = none in past 12 months.

* Multivariate analysis included centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Covariates included maternal education, maternal smoking, current diet, siblings. Adjusted for sex, region of the world, language, and gross national income. A total of 180,887 children were included from 77 centers in 36 countries.

old ISAAC study findings of acetaminophen use in infancy (24–27). Indeed, since publication of the earlier ISAAC findings, there have been a number of reports from prospective cohort studies that the association between acetaminophen use in early life and the risk of asthma in later childhood could be explained by confounding, due to the close association between acetaminophen use and respiratory morbidity in early childhood (28–30). Although such confounding is less likely to be relevant to the current use of acetaminophen in adolescent children, it may still be present to some extent. Another possibility is that there could be confounding by reverse causation if adolescents with asthma were more likely to develop febrile illnesses or experience pain and as a result have greater acetaminophen use than nonaffected adolescents. There do not appear to be data to assess this proposition for the wide range of febrile illnesses affecting adolescents worldwide, although those with asthma may be more prone to migraine, for which acetaminophen may be prescribed (31). However, there is evidence that acetaminophen may cause greater nasal symptoms and signs and a reduced serum neutralizing antibody response when taken for rhinovirus infection (32). This observation is relevant both to our study findings and to consideration of the nature of the association between acetaminophen use for respiratory tract infections in infancy and development of asthma in later childhood.

Another consideration is that in many countries, acetaminophen is marketed as the preferred analgesic and antipyretic of choice in persons with asthma. Although this has the potential to result in preferential use of acetaminophen, the observation that the association was present in populations with widely differing lifestyles, standard of living, medical practice, and availability of information of over-the-counter products containing acetaminophen suggests that it may not have had a major contribution to the association observed.

It is likely that adolescents who frequently took acetaminophen were more likely to have received acetaminophen in earlier childhood and the risk of asthma may have been due to this earlier use. This cannot be assessed in our study as only information on current use of acetaminophen was obtained, although it is relevant that in the previous ISAAC analysis the risk of current use of acetaminophen in 6- to 7-year-old children existed independently of acetaminophen use in the first year of life, and vice versa.

Potential confounding by factors that influence the risk of developing childhood asthma and use of acetaminophen is inherent in cross-sectional population-based studies. To address this issue, the ORs were adjusted for center level factors, such as region of the world, language, and gross national income, and multivariate analyses were undertaken in which potential confounding factors at the individual level were controlled for. In the multivariate analyses, there was no reduction in the strength of the association between acetaminophen use and asthma, suggesting that there was no major confounding by these factors. This pattern differs from that observed in the analyses from the 6- to 7-year-old children, in which the strength of the association was reduced in multivariate analyses, suggesting that confounding was present.

With these considerations in mind we propose that the findings are consistent with cross-sectional and longitudinal epidemiological studies, which have reported that acetaminophen exposure in the intrauterine environment, throughout childhood, and in adult life is associated with an increased risk of asthma (1–16). The findings are also consistent with the one randomized controlled trial of acetaminophen use in children with asthma (14). In that study, children with asthma were randomly assigned to receive either acetaminophen or ibuprofen during a febrile illness. Children randomized to acetaminophen had an increased risk of an outpatient visit for asthma, an effect which was observed for the treatment of fever due to respiratory but not other infective causes. However, as the study did not include a placebo treatment it was not possible to determine whether the observed difference in morbidity was attributable to an increased risk with acetaminophen treatment or a decreased risk with ibuprofen.

Our findings complement the international ecological analyses based on data from countries that participated in ISAAC Phase One and the European Community Respiratory Health Survey in which a positive association between per capita consumption and acetaminophen and the prevalence of asthma in children and adults, respectively, was reported (33). An observation from these studies is that English-speaking countries, which have among the highest prevalence rates of asthma, also have among the highest acetaminophen use, suggesting that greater acetaminophen use may explain to some extent the higher prevalence of asthma in English-speaking countries.

Overall, the population attributable risks for current symptoms of asthma and symptoms of severe asthma were around 40%, suggesting that if the associations were causal, they would

be of major public health significance. These compare with the population attributable risks of around 30% in the previous ISAAC study of 6- to 7-year-old children.

Similar to the findings in 6- to 7-year-old children, we observed an association between current acetaminophen use and current rhinoconjunctivitis and eczema symptoms in 13- to 14-year-old adolescents, and that this association was independent of the presence of asthma. These observations suggest that acetaminophen may have systemic inflammatory effects, possibly through increasing oxygen stress resulting from depletion of glutathione-dependent enzymes, which may also lead to enhanced Th2 allergic immune responses (1, 2, 15). Both mechanisms could lead to greater allergic inflammation, resulting in the development or worsening of preexisting asthma, rhinoconjunctivitis, or eczema, depending on the organ systems affected. Furthermore, acetaminophen may suppress the immune response to, and prolong the symptomatic illness from, rhinovirus infections (32), which are a common cause of severe exacerbations of asthma in childhood (34) and adult life (35) and in infancy are associated with an increased risk of subsequent asthma (36). Similarly, a recent study of prophylactic acetaminophen given at the time of vaccination illustrates that acetaminophen in routine antipyretic doses is capable of modulating immune responses (37).

In conclusion, the study findings add to the evidence that acetaminophen use in childhood may be an important risk factor for the development and/or maintenance of asthma. However, it is not possible in a study of this design to determine whether the positive association observed was causal. As a result, randomized controlled trials are now urgently required to investigate this relationship further and to guide the use of antipyretics not only in children but also in pregnancy and adult life.

Author Disclosure: R.W.B. was a consultant for and was on the Board or Advisory Board for GlaxoSmithKline ($5,001–$10,000) and Novartis ($1,001–$5,000). He received grant support from AztraZeneca, Novartis ($50,001–$100,000), and Chiesi ($10,001–$50,000). T.O.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.C. received grant support from Rex Medical (more than $100,001). C.K.W.L. was on the Board or Advisory Board of GlaxoSmithKline ($1,001–$5,000) and received lecture fees from AstraZeneca and GlaxoSmithKline ($1,001–$5,000). S.R.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.v.M. was a consultant for Protectimmun (up to $1,000) and was on the Board or Advisory Board for Novartis and GlaxoSmithKline ($1,001–$5,000). She received lecture fees from Novartis, GlaxoSmithKline, and ALK (up to $1,000). She received grant support from Airsonett AB ($10,001–$50,000) and received grant support from the European Commission, the German Research Foundation, and the Bavarian State Ministry (more than $100,001). A.W.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

ISAAC Phase Three Study Group

ISAAC Steering Committee: N. Aït-Khaled* (Union Internationale Contre la Tuberculose et les Maladies Respiratoires, Paris, France); H. R. Anderson (Department of Public Health Sciences, St Georges Hospital Medical School, London, UK); M.I. Asher (Department of Pediatrics, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand); R. Beasley* (Medical Research Institute of New Zealand, Wellington, New Zealand); B. Björkstén* (Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden); B. Brunekreef (Institute of Risk Assessment Science, Universiteit Utrecht, Netherlands); J. Crane (Wellington Asthma Research Group, Wellington School of Medicine, New Zealand); P. Ellwood (Department of Pediatrics, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand); C. Flohr (Centre for Evidence Based Dermatology, Queen's Medical Centre, University Hospital, Nottingham, UK); F. Forastiere (Department of Epidemiology, Rome E Health Authority, Italy); L. García-Marcos (Instituto de Salud Respiratoria, Universidad de Murcia, Spain); S. Foliaki* (Centre for Public Health Research, Massey University, Wellington, New Zealand); U. Keil* (Institut für Epidemiologie und Sozialmedizin, Universität Münster, Germany); C. K. W. Lai* (Department of Medicine and Therapeutics, The Chinese University of Hong Kong, SAR China); J. Mallol* (Department of Respiratory Medicine, University of Santiago de Chile, Chile); C. F. Robertson (Murdoch Children's Research Institute, Melbourne, Australia); E. A. Mitchell (Department of Pediatrics, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand); S. Montefort* (Department of Medicine, University of Malta, Malta); J. Odhiambo* (Centre Respiratory Diseases Research Unit, Kenya Medical Research Institute, Nairobi, Kenya); N. Pearce (Centre for Public Health Research, Massey University, Wellington, New Zealand); J. Shah* (Jaslok Hospital and Research Centre, Mumbai, India); A. W. Stewart (Population Health, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand); D. Strachan (Department of Public Health Sciences, St Georges Hospital Medical School, London, UK); E. von Mutius (Dr von Haunerschen Kinderklinik de Universität München, Germany); S. K. Weiland† (Department of Epidemiology, University of Ulm, Germany); G. Weinmayr (Institute of Epidemiology, University of Ulm, Germany); H. Williams (Centre for Evidence Based Dermatology, Queen's Medical Centre, University Hospital, Nottingham, UK); G. Wong (Department of Pediatrics, Prince of Wales Hospital, Hong Kong, SAR China). *Regional Coordinators. †Deceased March 2007.

ISAAC International Data Centre: M. I. Asher, T. O. Clayton, P. Ellwood, E. A. Mitchell, Department of Pediatrics: Child and Youth Health; and A. W. Stewart, School of Population Health, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand.

ISAAC Principal Investigators: Barbados: Dr. M. E. Howitt* (Barbados); Belgium: Prof. J. Weyler (Antwerp); Bolivia: Dr. R. Pinto-Vargas* (Santa Cruz); Brazil: Assoc. Prof. A. J. L. A. Cunha (Nova Iguaçu), Assoc. Prof. L. de Freitas Souza (Feira de Santana, Salvador, Vitória da Conquista); Cameroon: Prof. C. Kuaban* (Yaounde); Canada: Prof. A. Ferguson (Vancouver); Channel Islands: Dr. P. Standring (Guernsey); Chile: Dr. P. Aguilar (South Santiago), Dr. L. Amarales (Punta Arenas), Dr. L. A. V. Benavides (Calama), Dra. A. Contreras (Chiloe); China: Prof. Y.-Z. Chen* (Beijing, Tong Zhou), Assis. Prof. O. Kunii (Tibet), Dr. Q. Li Pan (Wulumuqi), Prof. N.-S. Zhong (Guangzhou); Colombia: Dr. G. Aristizábal (Bogotá), Dr. A. M. Cepeda (Barranquilla), Dr. G. A. Ordoñez (Cali); Cote d'Ivoire: Dr. B. N. Koffi* (Urban Cote d'Ivoire); Ecuador: Dr. C. Bustos (Guayaquil); Estonia: Dr. M.-A. Riikjärv* (Tallinn); Ethiopia: Assoc. Prof. K. Melaku (Addis Ababa); Fiji: Dr. R. Sa'aga-Banuve (Suva); Finland: Dr. J. Pekkanen* (Kuopio County); Former Yugoslav Republic of Macedonia (FYROM): Dr. E. Vlaski* (Skopje); Gabon: Dr. I. E. Hypolite* (Port-Gentil); Hong Kong: Prof. Y. L. Lau (Hong Kong, 6–7 yr age group), Prof. G. Wong (Hong Kong, 13–14 yr age group); Hungary: Dr. Z. Novák (Szeged), Dr. G. Zsigmond* (Svábhegy); India: Prof. S. Awasthi (Lucknow), Assoc. Prof. S. Bhave (Rasta Peth), Dr. N. M. Hanumante (Pune), Dr. K. C. Jain (Jodhpur), Dr. V. A. Khatav (Borivali), Dr. S. N. Mantri (Mumbai), Dr. A. V. Pherwani (Mumbai), Prof. S. Rego (Bangalore), Prof. M. Sabir (Bikaner), Dr. S. Salvi (Nagpur, Pimpri), Dr. G. Setty (Chennai), Prof. S. K. Sharma (New Delhi), Prof. V. Singh (Jaipur), Dr. T. U. Sukumaran (Kottayam), Dr. P. S. Suresh Babu (Davangere); Indonesia: Prof. Dr. C. B. Kartasasmita (Bandung), Prof. P. Konthen (Bali), Dr. W. Suprihati (Semarang); Iran: Dr. M.-R. Masjedi* (Rasht, Tehran); Japan: Dr. H. Odajima (Fukuoka); Kuwait: Dr. J. A. al-Momen (Kuwait); Kyrgyzstan: Dr. C. Imanalieva* (Balykchi, Bishkek); Lithuania: Assoc. Prof. J. Kudzyte* (Kaunas); Malaysia: Assoc. Prof. B. S. Quah (Kota Bharu), Dr. K. H. Teh (Alor Setar); Mexico: Dr. M. Baeza-Bacab* (Mérida), Dra. M. Barragán-Meijueiro (Ciudad de México), Dra. B. E. Del-Río-Navarro (Ciudad de México), Dr. R. García-Almaráz (Ciudad Victoria), Dr. S. N. González-Díaz (Monterrey), Dr. J. V. Merida-Palacio (Mexicali Valley), Dra. N. Ramírez-Chanona (Ciudad de México), Dr. S. Romero-Tapia (Villahermosa); Morocco: Prof. Z. Bouayad* (Boulmene, Casablanca, Marrakech); New Zealand: Prof. M. I. Asher* (Auckland), Dr. R. MacKay (Nelson), Dr. C. Moyes (Bay of Plenty), Assoc. Prof. P. Pattemore (Christchurch), Prof. N. Pearce (Wellington); Nigeria: Prof. B. O. Onadeko (Ibadan); Panama: Dr. G. Cukier* (David-Panamá); Peru: Dr. P. Chiarella* (Lima); Philippines: Prof. F. Cua-Lim* (Metro Manila); Poland: Assoc. Prof. A. Brêborowicz (Poznan), Assoc. Prof. G. Lis* (Kraków); Portugal: Dra. R. Câmara (Funchal), Dr. J. M. Lopes dos Santos (Porto), Dr. C. Nunes (Portimao), Prof. J. E. Rosado Pinto* (Lisbon); Samoa: Ms P. Fuimaono (Apia); South Africa: Prof. H. J. Zar* (Cape Town); South Korea: Prof. H.-B. Lee* (Provincial Korea, Seoul); Spain: Prof. A. Blanco-Quirós (Valladolid), Dr. R. M. Busquets (Barcelona), Dr. I. Carvajal-Urueña (Asturias), Dr. G. García-Hernández (Madrid), Prof. L. García-Marcos* (Cartagena), Dr. C. González Díaz (Bilbao), Dr. A. López-Silvarrey Varela (A Coruña), Prof. M. M. Morales-Suárez-Varela (Valencia), Prof. E. G. Pérez-Yarza (San Sebastián); Sudan: Prof. O. A. A. Musa (Khartoum); Sultanate of Oman: Assoc. Prof. O. Al-Rawas* (Al-Khod); Syrian Arab Republic: Dr. S. Mohammad* (Tartous), Prof. Y. Mohammad (Lattakia), Dr. K. Tabbah (Aleppo); Taiwan: Dr. J.-L. Huang* (Taipei), Dr. C.-C. Kao (Taoyuan); Tokelau: Dr. T. Iosefa* (Tokelau); USA: Dr. H. H. Windom (Sarasota); UK: Dr. M. Burr (Wales); Uruguay: Dra. D. Holgado* (Montevideo), Dra. M. C. Lapides (Paysandú); Venezuela: Dr. O. Aldrey* (Caracas).

ISAAC National Coordinators not identified above: Brazil: Prof. D. Solé; Canada: Prof. M. Sears; Chile: Dra. V. Aguirre; Colombia (interim): Prof. J. Mallol; Ecuador: Dr. S. Barba; Hong Kong: Dr. C. K. W. Lai; India: Dr. J. Shah; Isle of Man: Prof. R. Anderson; Japan: Prof. S. Nishima; Malaysia: Assoc. Prof. J. de Bruyne; Samoa: Dr. N. Tuuau-Potai; Sudan: Dr. A. El Sony.

References

1. Eneli I, Sadri K, Camargo C Jr, Bar RG. Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence. *Chest* 2005; 127:604–612.

2. Farquhar H, Stewart A, Mitchell E, Crane J, Eyers S, Weatherall M, Beasley R. The role of paracetamol in the pathogenesis of asthma. *Clin Exp Allergy* 2010;40:32–41.
3. Shaheen SO, Newson RB, Sherriff A, Henderson AJ, Heron JE, Burney PGJ, Golding J, and the ALSPAC Study Team. Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002;57:958–963.
4. Shaheen SO, Newson RB, Henderson AJ, Headley JE, Stratton FD, Jones RW, Strachan DP, and the ALSPAC Study Team. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005;35:18–25.
5. Perzanowski MS, Miller RL, Ali DB, Garfinkel RS, Chew GL, Goldstein IF, Perera FP, Barr RG. Prenatal acetaminophen exposure and risk of wheeze at age 5 years in an urban, low income cohort. *Thorax* 2010;65: 118–123.
6. Cohet C, Cheng S, MacDonald C, Baker M, Foliaki S, Huntington N, Douwes J, Pearce N. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. *J Epidemiol Community Health* 2004;58:852–857.
7. Rebordosa C, Kogevinas M, Sorensen HT, Olsen J. Prenatal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study. *Int J Epidemiol* 2008;37:583–590.
8. Wong GWK, Leung TF, Ma Y, Liu EKH, Yung E, Lai CKW. Symptoms of asthma and atopic disorders in preschool children: prevalence and risk factors. *Clin Exp Allergy* 2007;37:174–179.
9. Beasley R, Clayton T, Crane J, von Mutius E, Lai CKW, Montefort S, Stewart A, and the ISAAC Phase Three Study Group. 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. *Lancet* 2008; 372:1039–1048.
10. Shaheen SO, Sterne JAC, Songhurst CE, Burney PGJ. Frequent paracetamol use and asthma in adults. *Thorax* 2000;55:266–270.
11. Davey G, Berhane Y, Duncan P, Aref-Adib G, Britton J, Venn A. Use of acetaminophen and the risk of self-reported allergic symptoms and skin sensitization in Butajira, Ethiopia. *J Allergy Clin Immunol* 2005; 116:863–868.
12. Barr RG, Wentowski CC, Curhan GC, Somers SC, Stampfer MJ, Schwartz J, Speizer FE, Camargo CA Jr. Prospective study of acetaminophen use and newly diagnosed asthma among women. *Am J Respir Crit Care Med* 2004;169:836–841.
13. McKeever TM, Lewis SA, Smith HA, Burney P, Britton JR, Cassano PA. The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Respir Crit Care Med* 2005;171:966–971.
14. Lesko SM, Louik C, Vezina RM, Mitchell AA. Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics* 2002;109:e20.
15. Nuttall SL, Williams J, Kendall MJ. Does paracetamol cause asthma? *J Clin Pharm Ther* 2003;28:251–257.
16. Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW. The international study of asthma and allergies in childhood (ISAAC): phase three rationale and methods. *Int J Tuberc Lung Dis* 2005;9: 10–16.
17. Asher MI, Montefort S, Björkstén B, Lai CKW, Strachan DP, Weiland SK, Williams H, and the ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368:733–743.
18. Ellwood P, Williams H, Aït-Khaled N, Björkstén B, Robertson C, ISAAC Phase III Study Group. Translation of questions: the International Study of Asthma and Allergies in Childhood (ISAAC) experience. *Int J Tuberc Lung Dis* 2009;13:1174–1182.
19. Benichou J. A review of adjusted estimators of attributable risk. *Stat Methods Med Res* 2001;10:195–216.
20. Shaw RA, Crane J, Pearce N, Burgess CD, Bremner P, Woodman K, Beasley R. Comparison of a video questionnaire with the IUATLD written questionnaire for measuring asthma prevalence. *Clin Exp Allergy* 1992;22:561–568.
21. Lai CKW, Chan JKW, Chan A, Wong G, Ho A, Choy D, Lau J, Leung R. Comparison of the ISAAC video questionnaire (AVQ 3.0) with the ISAAC written questionnaire for estimating asthma associated with bronchial hyperactivity. *Clin Exp Allergy* 1997;27:540–545.
22. Gibson PG, Henry R, Shah S, Toneguzzi R, Francis JL, Norzila MZ, Davies H. Validation of the ISAAC video questionnaire (AVQ 3.0) in adolescents from a mixed ethnic background. *Clin Exp Allergy* 2000;30:1181–1187.
23. Anderson HR, Gupta R, Kapetanakis V, Asher MI, Clayton T, Robertson CF, Strachan DP, The ISAAC Steering Committee. International correlations between indicators of prevalence, hospital admissions and mortality for asthma in children. *Int J Epidemiol* 2008; 37:573–582.
24. Singh M. Paracetamol as a risk factor for allergic disorders. *Lancet* 2009; 373:119.
25. Lawrence J, Moore E, Port L, Danchin M, Connell T. Paracetamol as a risk factor for allergic disorders. *Lancet* 2009;373:119.
26. Lowe A, Abramson M, Dharmage S, Allen K. Paracetamol as a risk factor for allergic disorders. *Lancet* 2009;373:120.
27. Beasley R, Clayton T, Crane J, von Mutius E, Lai CKW. Paracetamol as a risk factor for allergic disorders. *Lancet* 2009;373:120–121.
28. Strippoli MF, Spycher BD, Beardsmore CS, Silverman M, Kuehni CE. Paracetamol use and the risk of wheeze: causation or bias? *Eur Respir J* 2009;34:230s.
29. Taipiainen T, Dunder T, Möttönen M, Pokka T, Uhari M. Adolescents with asthma or atopic eczema have more febrile days in early childhood: a possible explanation for the connection between paracetamol and asthma. *J Allergy Clin Immunol* 2010;1215:751–752.
30. Lowe A, Carlin J, Bennett C, Hosking C, Allen K, Robertson C, Axelrad C, Abrahmson M, Hill D, Dharmage S. Does paracetamol in early life cause asthma? *Respirology* 2010;15:A24.
31. Davey G, Sedgwick P, Maier W, Visick G, Strachan DP, Anderson HR. Association between migraine and asthma: matched case-control study. *Br J Gen Pract* 2002;52:723–727.
32. Graham NMH, Burrell CH, Douglas RM, Debelle P, Davies L. Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. *J Infect Dis* 1990;162:1277–1282.
33. Newson RB, Shaheen SO, Chinn S, Burney PGJ. Paracetamol sales and atopic disease in children and adults: an ecological analysis. *Eur Respir J* 2000;18:817–823.
34. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, O'Toole S, Myint SH, Tyrrell DA, *et al.* Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995;310:1225–1229.
35. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *BMJ* 1993;307:982–986.
36. Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, Kirk CJ, Reisdorf E, Roberg KA, Anderson EL, *et al.* Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005;116:571–577.
37. Prymula R, Siegrist C-A, Chlibek R, Zemlickova H, Vackova M, Smetana J, Lommel P, Kaliskova E, Borys D, Schuerman L. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet* 2009;374:1339–1350.