

Use of acetaminophen and the risk of self-reported allergic symptoms and skin sensitization in Butajira, Ethiopia

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Background: Studies in developed countries suggest that acetaminophen use is associated with increased risk of asthma, but it is unclear whether this association is causal.

Objective: To determine the relation among acetaminophen use, asthma, and allergy, and to explore potential biases in acetaminophen use, in a developing country population.

Methods: We surveyed 7649 adults and children from Butajira, Ethiopia, collecting data on self-reported symptoms of allergic disease, skin sensitization to *Dermatophagoides pteronyssinus* and cockroach, acetaminophen use, and potential confounders. We then collected detailed data on indications for acetaminophen use and reasons for aspirin avoidance in a nested follow-up study.

Results: Allergic symptoms increased significantly with frequency of acetaminophen use, with odds ratios in those using >3 tablets in the past month relative to none 1.89 (95% CI, 1.51-2.36) for wheeze, 2.14 (1.72-2.67) for nocturnal shortness of breath, 2.52 (1.99-3.20) for rhinitis, and 1.90 (1.39-2.61) for eczema. Cockroach sensitization was also more common in the highest acetaminophen category (odds ratio, 1.40; 95% CI, 1.10-1.79), but *D pteronyssinus* sensitization was not. Less than 1% of participants with asthma or wheeze in our nested study reported avoidance of aspirin because of asthma symptoms. None volunteered using acetaminophen to treat allergic symptoms.

Conclusion: There is a dose-related association between acetaminophen use and self-reported allergic symptoms in this population that is not a result of aspirin avoidance, reverse causation, or other bias. Acetaminophen may therefore be involved in the etiology of asthma and allergic disease. (J Allergy Clin Immunol 2005;116:863-8.)

Key words: Acetaminophen, allergic sensitisation, aspirin, asthma, developing country, eczema, Ethiopia, paracetamol, rhinitis

Abbreviation used
OR: Odds ratio

Evidence is accumulating that use of acetaminophen (paracetamol) may increase the risk of asthma and other allergic disease. In an international ecological study, acetaminophen sales were correlated with the prevalence of asthma, eczema, and rhinitis in children and/or adults¹; a case-control study of adults in the United Kingdom demonstrated an exposure-response association between acetaminophen intake and self-reported asthma symptoms²; and a survey from New Zealand reported associations between acetaminophen use and wheezing, asthma, eczema, and rhinitis in children.³ Recently, a cross-sectional analysis of adults from the National Health and Nutrition Examination Survey III survey showed acetaminophen to be related to an increased risk of asthma and chronic obstructive pulmonary disease and to reduced lung function,⁴ and a prospective study of United States nurses showed a positive association between acetaminophen use and newly diagnosed asthma.⁵ Associations between frequent maternal use of acetaminophen in late pregnancy and wheeze, asthma, and IgE in children have also been reported.^{6,7} It is biologically plausible that acetaminophen might predispose to asthma through depletion of glutathione and consequent reduced antioxidant capacity.⁸⁻¹⁰

However, nearly all of the available evidence is derived from economically developed countries and is susceptible to bias arising from the medical contraindication to use of aspirin or other nonsteroidal anti-inflammatory drugs in asthma.¹¹ However, this and other possible mechanisms of reverse causation, such as treatment of headache caused by asthma therapy, are much less likely to have a strong influence in developing countries, where awareness of adverse effects of aspirin and use of medication to treat asthma are both relatively low. We have therefore tested the hypothesis that acetaminophen use is associated with an increased risk of allergic symptoms and sensitization in a cross-sectional survey of adults and children from Butajira, in southern Ethiopia. We have also investigated potential bias, confounding, and reverse causation in qualitative and quantitative follow-up studies.

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METHODS

The Butajira Rural Health Project is a dynamic cohort with an established data collection system covering more than 40,000 people living in 10 administrative areas (1 urban, 9 rural) of Meskan and Mareko district, 130 km southwest of Addis Ababa in Ethiopia. The source population, initial sampling procedure, and basic population characteristics of this cohort have been described in detail elsewhere.¹²

As part of an investigation into the relationship among wheeze, asthma, and parasite infection,¹³ we randomly selected 4300 individuals from the urban area, and sampled 4591 individuals from the rural districts by selecting every 7th subject age 5 years or older in the Butajira Rural Health Project starting from a random start point. To deal with the attrition we encountered in the urban sample during the study because of outmigration arising from a recent drought, fieldworkers were instructed to substitute urban individuals who had left the area with someone of the same sex and within 5 years of age living in the same or adjacent household. Fieldworkers took written consent and measured allergen skin sensitization to *Dermatophagoides pteronyssinus* and cockroach (Biodiagnostics, Upton-upon-Severn, United Kingdom) by lifting the dermis with a sterile needle tip through a drop of each solution applied to the palmar surface of the forearm. They administered a questionnaire including standardized respiratory questions¹⁴ shown to predict bronchial hyperreactivity in other populations¹⁵: "Have you had wheezing or whistling in your chest at any time in the last year?" "Have you been woken by an attack of shortness of breath at any time in the last year?" and, "Have you ever had asthma? If yes, have you had an attack of asthma in the last year?" Questions were also included on rhinitis and eczema symptoms: "Have you ever had hayfever or persistent sneezing attacks? If yes, has this occurred in the last year?" "Have you ever had an itchy skin rash which has affected the skin creases (eg, the folds of the elbow or behind the knees) at some stage? If yes, has this rash been present in the last year?" Questions on potential confounders, including occupation, level of education, income (these 3 questions were asked in relation to the father in children age 12 years or younger), duration of breast-feeding, birth order, family size, ownership of consumer goods, sanitation, active and passive smoking, vaccination history, ethnic group, construction of house, domestic fuel use, bedding material, insecticide use, and animals in the house were also included. Respondents were asked whether they had taken acetaminophen in the previous month, and if so, whether 3 or fewer tablets, 4 to 30 tablets, or more than 30 tablets. Boxes and strips of the locally available acetaminophen formulations were used as prompts. All questions were asked through a parent or adult caretaker for children age 12 years or younger. Fieldwork was conducted between February and June 2003. In accordance with the main objective of the study, all participants were asked to provide a fecal sample for parasite egg counting.¹³

Nested study

After initial analysis of the relation between acetaminophen use on asthma risk in the cross-sectional survey, we then designed and performed a nested study of potential biases in the use of acetaminophen within the study population. To inform the design of our study instruments, we first performed 8 focus group discussions in prescribers, dispensers, urban and rural men and women, and men and women with asthma and/or allergic symptoms. These explored recognition and perceived indications and contraindications to use of aspirin and acetaminophen. We used this information to design a questionnaire-based interview in which respondents were asked to distinguish acetaminophen and aspirin, and then asked in detail about frequency and quantity of use of each drug, symptoms for

use, avoidance, adverse effects, contraindications, local cost and availability, and preference for acetaminophen or aspirin. The questionnaire also included questions on the use of any asthma medications and their perceived side effects. In July 2004 we used this questionnaire to survey selected subsamples from our study participants living in Butajira town and the 4 rural areas that were accessible during the rains. These subsamples were composed of a random subsample of 250 from all participants in these areas (which represented the general study population and hence included some individuals with reported allergic symptoms); a random subsample of 200 of the 353 subjects with wheeze and/or asthma, but not eczema or rhinitis, in the past year; a random subsample of 200 of the 272 subjects with rhinitis, but not eczema, wheeze, or asthma, in the past year; and all 122 subjects with eczema, but not rhinitis, wheeze, or asthma, in the past year. None of these subjects had taken part in the earlier focus group discussions. Approval for all studies was granted by the relevant local ethics committees in Addis Ababa and Nottingham.

Statistical analysis

Data were entered into EPI-Info (version 6; CDC, Atlanta, Ga) and exported into SPSS (version 11; SPSS Inc, Chicago, Ill) for analysis. The primary outcome variables were self-reported wheeze, shortness of breath at night, rhinitis and eczema in the past year, self-reported asthma ever, and allergic skin sensitization to *D pteronyssinus* and cockroach. A positive skin test was defined as an average of 2 perpendicular wheal diameters of at least 3 mm greater than the saline control response. Multiple logistic regression was used to determine the independent effect of acetaminophen use on each outcome, controlling for potential confounding by age, sex, area of residence, smoking, educational level, and presence of any parasite. To assess whether effects of acetaminophen differed between urban and rural residents, or between children age younger than 15 years and adults, interaction terms were fitted to the models.

Using data from the nested study, we estimated the proportion of individuals in each category of acetaminophen use who might be taking acetaminophen for symptoms of allergic disease, through avoidance of aspirin because of their condition, or for side effects of asthma treatment. Then, taking each allergic disease subsample as our case group, and those subjects from the random subsample without allergic disease as controls, odds ratios (ORs) were derived in relation to acetaminophen intake before and after exclusion of individuals taking acetaminophen for reasons related to their allergic condition. Results presented from the nested study are adjusted for age, sex, area of residence, smoking, and educational level only, because missing data on parasite infection substantially reduced power when this variable was included. The effect of further control for parasites on the magnitude of the ORs was explored, however.

RESULTS

Questionnaire and skin test data were obtained from 7649 (3485 urban and 4164 rural) individuals. The urban participants were 2679 of the original sample of 4300, and 806 substitutions for individuals who had left the area, giving a net response of 81%. The response in the rural area was 91%. The median age of participants was 20 (range, 5-95 years), and 3252 (42.5%) participants were male. A full description of the demographics of participants and comparison with source population is reported elsewhere.¹³ The 12-month prevalence of wheeze was

10.5% (802/7649); shortness of breath, 11.0% (842/7649); rhinitis, 8.8% (674/7628); and eczema, 4.2% (323/7634). Asthma ever was reported by 2.0% of respondents (146/7345), of whom 109 reported an attack in the past year. The prevalence of positive skin sensitization was 10.8% (824/7649) for *D pteronyssinus* and 8.2% (629/7649) for cockroach. Rhinitis and eczema were strongly related to one another (OR, 3.79; 95% CI, 2.91-4.94; $P < .001$) and to wheeze (wheeze and rhinitis, OR, 4.18; 95% CI, 3.47-5.04; wheeze and eczema, OR, 2.55; 95% CI, 1.94-3.35; both $P < .001$). Further details of the prevalence and relation of wheeze, asthma, and sensitization are documented elsewhere.¹³

Acetaminophen use

Acetaminophen had been used in the last month by 3219 (42%) respondents, 2360 (30.9%) consuming 3 or fewer tablets, 841 (11%) between 4 and 30 tablets, and 18 (0.2%) more than 30 tablets. The latter 2 categories were combined for further analysis. Univariate analysis showed no significant difference in acetaminophen use between urban and rural residents, between male and female subjects, or across education levels (Table I). However, acetaminophen use was more common among adults, smokers, and those not infected with parasites (Table I).

Acetaminophen use, allergic symptoms, and sensitization

The prevalence of each outcome increased in relation to increasing category of acetaminophen use, with the exception of cockroach sensitization, which was increased in the highest dose category only. After adjustment for age, sex, area of residence, presence of any parasite, smoking status, and educational level, statistically significant dose-response relations were seen for wheeze, shortness of breath at night, eczema, and rhinitis (P for trend $< .001$; Table II). ORs for more than 3 tablets in the past month compared with none ranged from 1.89 for wheeze to 2.52 for rhinitis. The adjusted odds of cockroach sensitization were also significantly increased in those consuming more than 3 tablets of acetaminophen a month relative to none, by a ratio of 1.40 (95% CI, 1.10-1.79), but there was no significant adjusted association between acetaminophen use and either self-reported asthma or dust mite sensitization (Table II). Adjustment for other demographic and lifestyle variables collected made little difference to the strength or significance of any of these associations. Similarly, control for cockroach sensitization had very little effect on the allergic symptoms ORs. There was no evidence of effect modification by area of residence or by age, with the exception of cockroach sensitization, with the effect of acetaminophen dose on cockroach sensitization significantly stronger among rural residents and children (data not shown).

Restriction of analysis to people without self-reported asthma resulted in similar or slightly stronger associations

TABLE I. Use of acetaminophen in the past month by demographic and lifestyle factors

	N	N (%) using acetaminophen	P value
All subjects	7649	3219 (42.1%)	
Area of residence			.22
Urban	3485	1440 (41.3%)	
Rural	4164	1779 (42.7%)	
Sex			.15
Male	3252	1338 (41.1%)	
Female	4397	1881 (42.8%)	
Age, y			
5-9	1158	307 (26.5%)	
10-19	2645	1058 (40.0%)	
20-29	1253	590 (47.1%)	
30-39	1021	525 (51.4%)	<.001
40-49	659	323 (49.0%)	
50-59	391	182 (46.5%)	
60-69	325	153 (47.1%)	
70+	197	81 (41.1%)	
Any parasite			.04
Yes	2332	941 (40.4%)	
No	4568	1964 (43.0%)	
Smoking status			.005
Ever smoker	240	122 (50.8%)	
Never smoker	7409	3097 (41.8%)	
Education level*			
Unable to read or write	3443	1419 (41.2%)	
Read or write only	1127	470 (41.7%)	
Grade 1-6	1757	777 (44.2%)	.30
Grade 7-12	1134	471 (41.5%)	
Higher education	186	82 (44.1%)	

*Education level of respondent, or father if respondent age 12 or younger.

with acetaminophen use (adjusted ORs for more than 3 tablets compared with none, 1.88 [95% CI, 1.47-2.40] for wheeze; 2.25 [1.78-2.86] for shortness of breath; 1.93 [1.37-2.70] for eczema; 2.81 [2.16-3.67] for rhinitis; 1.38 [1.07-1.79] for cockroach sensitization).

Nested study

The follow-up questionnaire was completed by 204 (82%) of the general population subsample, 101 (83%) of the eczema group, 176 (88%) of the rhinitis group, and 161 (81%) of the wheeze/asthma group. None of the respondents with allergic disease symptoms volunteered using acetaminophen for their allergic symptoms. Only 7 subjects in the wheeze/asthma group reported taking any asthma therapy, and of the 117 subjects in the wheeze/asthma group who could discriminate between acetaminophen and aspirin, 1 participant reported avoidance of aspirin and acetaminophen on the grounds that they both made the participant's asthma worse. There were no other reports of aspirin avoidance for reasons relating to asthma, eczema, or rhinitis.

In a case-control analysis of participants of the nested study, which compared cases of wheeze/asthma with the 160 subjects from the general population sample with no

TABLE II. Allergic outcomes in relation to quantity of acetaminophen used

Outcome	Acetaminophen dose	N (%)	Adjusted OR* (95% CI)	Overall <i>P</i> value*	<i>P</i> for trend*
Wheeze (past year)	None	394 (8.9)	1.00	<.001	<.001
	1-3/mo	264 (11.2)	1.26 (1.06-1.50)		
	>3/mo	144 (16.8)	1.89 (1.51-2.36)		
Asthma (ever)	None	71 (1.7)	1.00	.26	.17
	1-3/mo	52 (2.3)	1.36 (0.93-1.99)		
	>3/mo	23 (2.9)	1.28 (0.76-2.15)		
Shortness of breath (past year)	None	392 (8.8)	1.00	<.001	<.001
	1-3/mo	298 (12.6)	1.48 (1.24-1.75)		
	>3/mo	152 (17.7)	2.14 (1.72-2.67)		
Eczema (past year)	None	162 (3.7)	1.00	<.001	.001
	1-3/mo	97 (4.1)	1.08 (0.83-1.42)		
	>3/mo	64 (7.5)	1.90 (1.39-2.61)		
Rhinitis (past year)	None	291 (6.6)	1.00	<.001	<.001
	1-3/mo	246 (10.4)	1.82 (1.50-2.19)		
	>3/mo	137 (16.0)	2.52 (1.99-3.20)		
Dust mite sensitization	None	453 (10.2)	1.00	.45	.26
	1-3/mo	258 (10.9)	1.03 (0.86-1.22)		
	>3/mo	113 (13.2)	1.17 (0.92-1.48)		
Cockroach sensitization†	None	357 (8.1)	1.00	<.001	.21
	1-3/mo	168 (7.1)	0.81 (0.66-0.99)		
	>3/mo	104 (12.1)	1.40 (1.10-1.79)		

*ORs adjusted for age, sex, area of residence, presence of any parasite, smoking status, and educational level; *P* values refer to adjusted analyses.

†Significant interactions between acetaminophen and area of residence, and between acetaminophen and age.

allergic symptoms, the OR for wheeze (adjusted for age, sex, area, smoking status, and educational level) in those in the highest acetaminophen intake category was 2.10 (95% CI, 1.03-4.26; *P* for trend across the categories, .03). After excluding the 7 patients using any asthma therapy (1 of whom was also the subject who avoided aspirin), this OR remained similar at 1.94 (95% CI, 0.95-3.98; *P* for trend, .049). Further adjustment for parasite infection had little effect on the magnitude of these ORs (2.05 and 1.88 before and after exclusion, respectively).

DISCUSSION

This study has demonstrated significant and consistent dose-related associations between acetaminophen use and reported symptoms of asthma, eczema, rhinitis, and 1 of 2 common local environmental allergens tested for skin sensitization. The study also demonstrates that these findings do not arise from use of acetaminophen to treat symptoms of allergic disease, from systematic avoidance of aspirin by individuals with allergic symptoms, or from use of acetaminophen to treat symptoms arising as adverse effects of asthma therapy. The study shows that even in this developing country population, use of simple analgesics was widespread, with 42% having used acetaminophen in the last month. This frequency of use is similar to that reported by asthma patients (46%) and controls (36%) in the South London study.² However 21% of patients and 13% of controls in that study had used acetaminophen on a weekly or daily basis,² demonstrating higher average

consumption than the current study population, of whom only 11% had used more than 3 tablets in the past month.

There was no significant relation between acetaminophen and self-reported asthma in the current study, but this is almost certainly a result of underdiagnosis of asthma in our study population, particularly in the rural areas where access to health facilities is limited. However, effects on self-reported symptoms of allergic disease as measured in our study are not influenced by this diagnostic bias, and the presence of strong and dose-related effects that were of similar magnitude for all outcomes suggests a general effect on allergic disease expression. Self-reported wheeze and waking at night with shortness of breath are both strongly associated with clinically diagnosed hyperresponsiveness in developed countries,¹⁵ indicating that our findings are likely to be directly relevant to the etiology of asthma. Although the validity of our allergic symptom questions has not been assessed in this population, there was considerable overlap between these symptoms, suggesting that they were all caused predominantly by allergic disease.

Previous reported evidence of an association between acetaminophen use and asthma symptoms has been potentially, though not necessarily, biased by 1 of more of the following influences. First, acetaminophen is used preferentially as a minor analgesic by people with asthma because of the recognized potential of aspirin to exacerbate asthma. Second, acetaminophen use may be increased by the occurrence of headache arising from asthma therapy (particularly β -agonists). Third, people with asthma may use acetaminophen to treat asthma symptoms. We investigated these influences in our nested

study and found all to be unlikely explanations for our main study findings. Awareness of the potential dangers of aspirin use in asthma was low in the Butajira area, with only 1 of our nested sample of those with wheeze or asthma reporting avoidance of aspirin. The contraindication to using aspirin in asthma that is widely recognized, at least among healthcare professionals, in developed countries is thus not a major influence in this population. It is also highly unlikely that acetaminophen use was increased in people with wheeze as a result of adverse effects of asthma therapy, because only 4% of those with wheeze and/or asthma were taking any asthma medication. This reflects the fact that in Ethiopia, 1 year of guideline-based medication for moderately severe asthma has been estimated to exceed the 6-month salary of a junior nurse, and imported treatments including inhaled salbutamol and beclomethasone are often out of stock even in Addis Ababa, the capital city.¹⁶ Furthermore, exclusion of people with asthma from our analyses made no major difference to the magnitudes of the acetaminophen effects. The fact that none of our nested study participants volunteered that they used acetaminophen for wheeze, cough, or shortness of breath indicates that it is unlikely that the association with wheeze in our study was a result of use of acetaminophen for airway symptoms. Our study population also excluded very young children, who represent the group most likely to develop wheeze as a consequence of viral infection rather than allergic asthma. All of this evidence indicates that the associations we report, as previously suggested,² are unlikely to have arisen from reverse causation.

Current rhinitis symptoms were associated with acetaminophen use in a dose-related manner with adjusted ORs of 1.82 for 1 to 3 tablets per month and 2.52 for 4+ tablets a month, similar to those reported by Shaheen et al² in adults in the United Kingdom (1.80 and 2.33 for weekly and daily use, respectively) and by Cohet et al³ in New Zealand children (1.77 for at least monthly use). We also found current eczema to be significantly associated with acetaminophen use in a dose-related manner, consistent with the ecological study that found significant associations between per capita acetaminophen sales and 12-month prevalence of eczema in children at least as strong as those for rhinitis.¹ Cohet et al³ looked at eczema ever in children 6 to 7 years old and found an increased risk with acetaminophen use in the first year of life, but not more recent use. Our observed associations for rhinitis and eczema were present among those both with and without self-reported wheeze (data not presented), suggesting that these effects are independent of asthma. We found no evidence that subjects with rhinitis or eczema avoided aspirin because of, or took acetaminophen for, their symptoms.

We find it difficult to explain why in this study cockroach sensitization was significantly associated with acetaminophen use, whereas dust mite sensitization was not. The European Community Respiratory Health Survey demonstrated a nonsignificant tendency to higher prevalence of skin sensitization among adults in centers with

higher acetaminophen sales,¹ but this study did not present data on individual allergens. The authors suggested that this might reflect a relatively modest promotion of general atopy through promotion of T_H2-type responses, but this would not explain sensitization to one allergen but not another.

Outmigration from Butajira town, arising from a recent drought, led to substitution of 806 selected urban residents with people of the same sex and age within 5 years currently living in the selected house. If recent immigrants differed from the original sample in characteristics related to acetaminophen use or risk of asthma or allergic symptoms, then bias might have resulted. However, prevalence of all main outcome variables was not significantly different between those in the original sample and substitutes, with the exception of those reporting wheeze in the past year, which was slightly less common among substitutes (8.4% compared with 10.7%; $P = .05$). Acetaminophen use was also not significantly different between these 2 groups.

The possibility of confounding in this study also needs consideration. We tried adjusting for several different markers of social affluence, including education level, income, ownership of consumer goods, and occupation, as well as numerous other potential confounders, and found that our associations persisted. Furthermore, the lack of difference in acetaminophen consumption between urban and rural areas suggests that use is not related to a more Western lifestyle in this population. Although confounding by some other factor not measured in this study cannot be ruled out, it seems unlikely that this would be responsible for the large size of effects seen.

This study has therefore demonstrated consistent, significant dose-response associations between acetaminophen use and a range of allergic symptoms and sensitization to cockroach in a population in which many of the alternative explanations previously raised have been shown not to operate. The fact that we have found results so similar to those previously reported in developed country populations makes it more likely that these associations reflect an important influence on the etiology of allergic disease. Biological mechanisms that may explain an association between acetaminophen and atopy include faulty glutathione-dependent processing of disulfide bonds¹⁷ and, thus, impaired antigen processing, resulting in T2 allergic pathways predominating.¹⁸ Alternatively, acetaminophen may promote T2 allergic pathways through stimulating COX-2 activity and increasing the production of prostaglandin E₂.¹⁹ The combination of epidemiological evidence for a link between acetaminophen and allergy, and plausible biological explanations for such a link, is powerful and calls for further investigation.

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of results for all stages of the study, as well as the writing of the manuscript. G. Davey supervised the data collection. Y. Berhane was involved in the study design and interpretation of data. P. Duncan and G. Aref-Adib were involved in the design, data collection, analysis, and interpretation of the follow-up studies (focus groups and nested questionnaire survey). All authors helped finalize the manuscript.

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