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Is Acetaminophen Use Associated with Atopic Eczema and other Allergic Diseases in Adolescents?

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ABSTRACT

Atopic Eczema (AE) is a chronic inflammatory skin disease that affects children and adults, and alters quality of life. Previous studies have suggested several socio-demographic and environmental factors related to the prevalence of AE and other allergic diseases, including acetaminophen use. In the present study, we report the rates of isolated AE, AE associated with asthma and AE associated with rhinitis among 13- to 14-year-old Spanish adolescents and the level of association of these conditions with the use of acetaminophen. We analyzed Spanish data from a cross-sectional Phase 3 study within ISAAC. A total of 28,717 adolescents completed the Phase 3 written questionnaire by answering questions for acetaminophen use and on asthma, rhinitis and AE symptoms.

We observed an association between acetaminophen use and AE among the adolescents who had used acetaminophen in the previous month. Furthermore, the prevalence rate increased with the number of allergic processes: for AE alone, the adjusted Prevalence Ratio (aPR) was 1.81 and for AE associated with rhinitis or with asthma, aPRs were 2.20 and 3.03, respectively.

We conclude that acetaminophen use in childhood may be an important factor associated with development and/or maintenance of AE and other allergic diseases.

Keywords: Acetaminophen; Adolescents; Asthma; Atopic Eczema; Rhinitis

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INTRODUCTION

The International Study of Asthma and Allergies in Childhood (ISAAC) has enabled a standardized worldwide assessment of self-reported asthma, rhinitis and atopic eczema (AE) symptoms in adolescents to provide a framework for etiological research into the genetic, lifestyle, environmental and medical care factors affecting these disorders.¹ ISAAC data have suggested several socio-demographic and environmental factors related to the prevalence of asthma and allergic diseases, including gender,² being overweight or obese,³ socio-economic status,⁴ migration,⁵ physical activity and time spent watching television,⁶ acetaminophen (paracetamol) use,⁷ exposure to traffic-related air pollution,⁸ environmental tobacco smoke,⁹ pet ownership¹⁰ and use of gas for cooking.¹¹

Along these lines, there is accumulating evidence that the risk of developing asthma may increase by acetaminophen use and, moreover, that the higher prevalence of asthma observed in various countries in recent decades may be attributed to a widespread growth in the use of this drug.¹²⁻¹⁴ This evidence stems primarily from epidemiological studies, which have reported that exposure to acetaminophen in the intrauterine environment,¹⁵⁻¹⁹ childhood,^{18,20,21} and adult life²²⁻²⁵ is associated with increased risk of asthma. There was also a randomized controlled trial which found increased rates of hospital visits for asthma in children who had taken acetaminophen compared with ibuprofen.²⁶ The potential mechanisms for these effects of acetaminophen include oxidant-induced airway inflammation and enhanced Th2 responses.^{12,13,27}

We conducted Phase 3 in eleven different geographical regions to obtain a comprehensive estimate of the burden of these allergic diseases in Spain. In this study, we report the rates of isolated AE, AE associated with asthma, AE associated with rhinitis among 13- to 14-year-old Spanish adolescents, as well as the level of association of these conditions with the use of acetaminophen.

MATERIALS AND METHODS

Study Design

The ISAAC Phase 3 methodology and protocol

have been described in detail elsewhere.²⁸ It was expected to involve around 90% of potential participants in each geographical region in order to detect differences in prevalence of 2% between regions with a 1% level of significance.

Participating Geographical Regions

We analyzed Spanish data from cross-sectional Phase 3 studies within ISAAC, conducted by eleven Spanish geographical regions (Asturias, Barcelona, Bilbao, Cartagena, Castellon, La Coruña, Madrid, Pamplona, San Sebastián, Valencia and Valladolid). Simple random sampling was used to select the schools invited to participate. Of a total of 30,046 adolescents, 28,717 met the inclusion criteria for this study (Figure 1).

In each geographical region, researchers recruited participants from randomly selected schools. Adolescents were recruited from ESO classes (corresponding to the first four years of secondary education) as these have the highest proportion of 13- to 14-year-olds.

Questionnaires

Each participant completed the Phase 3 written questionnaire by answering key questions for asthma, rhinitis and AE symptoms.^{28,29}

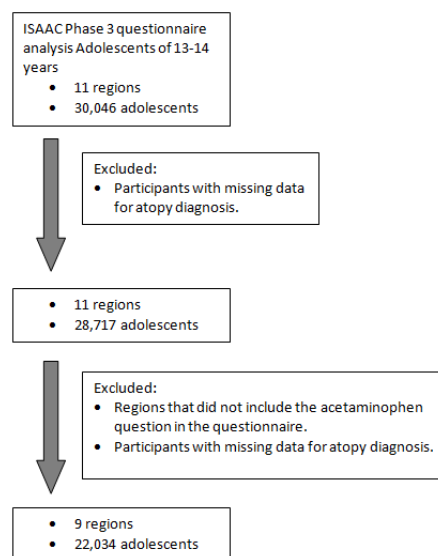


Figure 1. Flow diagram of the inclusion of regions and adolescents

Acetaminophen Use and Atopy in Adolescents

The question used to determine prevalence of current wheezing was: "Have you had wheezing or whistling in the chest in the past 12 months?" Current rhinitis was defined by positive answers to the following two questions: "Have you had problems with sneezing, or a runny, or blocked nose when you did not have a cold or the flu in the past 12 months?" and "Has this nose problem been accompanied by itchy watery eyes?" Three questions were used to assess the prevalence of current AE: "Have you ever had an itchy rash that came and went for at least 6 months?"; if so, "Have you ever had this itchy rash at any time in the past 12 months?" and, finally, if so, "Has this itchy rash at any time affected any of the following places: your elbow creases, behind your knees, the front of your ankles, under your buttocks or around your neck, ears or eyes?".¹⁹

The question relating to acetaminophen use was: "In the past 12 months, how often on average have you taken acetaminophen (paracetamol) (e.g., Panadol, Pamol)?" Never/At least once a year/At least once per month.¹⁹

This questionnaire also included questions about demographics, mother's level of education, household smoking and use of acetaminophen; all these questions were answered by all the adolescents.

The study protocol for ISAAC Phase 3 was approved by the Research Ethics Boards of the home institutions of all of the research centers. With the collaboration of schools and the approval of parents, adolescents completed the questionnaires during school hours.

Data Analysis

The data from each geographic region were double-entered into the database. We calculated the absolute frequency, and the crude and adjusted prevalence ratios (cPR and aPR) using contingency tables, as well as 95% confidence intervals (95% CI). For aPR, acetaminophen consumption was used as the independent variable and the mother's type of education and household smoking were employed as dependent variables. Differences were considered significant for $p < 0.05$.

RESULTS

Data Collection

The characteristics of the participating geographical

regions, sampling frames, response rates and sample sizes are listed in Table 1. In all, 28,717 adolescents from eleven Spanish cities (regions) participated in this study.

Prevalence of Diagnosed Atopic Eczema (AE), Asthma and Rhinitis per Region

Table 2 shows the prevalence of diagnosed AE, asthma and rhinitis according to region.

We observed that, at the time of the study, the overall rate of AE in the eleven geographical regions was 13.2%. Prevalence of AE alone was 8.6% (2,482 adolescents), representing 65% of those affected by AE (3,798). The remaining adolescents (1,316) were split evenly between AE associated with asthma, with rhinitis, and with both AE and rhinitis, with rates of 1.5% (429), 1.6% (468) and 1.5% (419), respectively.

Demography, Environmental Characteristics and Acetaminophen Consumption

Of the 28,717 adolescents studied, there was a significant difference in total AE prevalence for gender, with 59.9% of those affected being female. The rates of AE alone and AE associated with rhinitis also significantly differed between genders, with 37.7% and 40.3% of cases being males, respectively. No significant differences of AE prevalence were found between the different age groups studied (13 vs. 14 years) (Table 3).

When considering acetaminophen use, the overall AE rate was higher among adolescents who had consumed this drug in the previous year. Moreover, AE associated with asthma and rhinitis was seen to be more prevalent in adolescents who had consumed acetaminophen in the previous month.

We found a significant association between AE and use of acetaminophen: of the 2,482 adolescents suffering from AE, 978 (51.2%) had used acetaminophen in the previous year and 695 (36.4%) in the previous month, while only 12.4% (237) of the adolescents reporting AE also stated never having used this drug (Table 3).

AE Prevalence According to Current Acetaminophen Use

A stronger association was found between acetaminophen use and AE among the adolescents who reported taking acetaminophen at least once in the previous month compared to those who had stated

consuming it at least once in the previous year.

Furthermore, the prevalence rate increased with the number of allergic processes: for AE alone, the aPR was 1.81; for AE associated with rhinitis or with asthma, the aPRs were 2.20 and 3.03, respectively; for

AE associated with both asthma and rhinitis, the aPR was markedly higher (10.08). In all, the association was stronger among adolescents who had used acetaminophen at least once in the previous month (all $p < 0.001$) (Table 4).

Table 1. The ISAAC III regions in Spain, the study population of adolescents aged 13-14 years old and participation rate percentage

Region	Response rate (%)	Potential participants, no.	Sample size, no.
Asturias	90.2	4186	2796
Barcelona	87.7	2784	2610
Bilbao	88.2	3397	2717
Cartagena	75.8	3995	2688
Castellón	91.2	4025	3799
La Coruña	93.7	2981	2493
Madrid	88.7	2647	2439
Pamplona	96.8	2932	2566
San Sebastián	94.9	1085	1030
Valencia	78.7	3133	2947
Valladolid	100.0	2947	2632
Total	88.6	30046	28717

Table 2. Prevalence of diagnosed AE according to region in adolescents aged 13-14 years

Region	AE		AE+A		AE+R		AE+A+R		AE total	
	N	Prev (%)	N	Prev (%)	N	Prev (%)	N	Prev (%)	N	Prev (%)
Asturias	186	6.7	53	1.9	47	1.7	40	1.4	326	11.7
Barcelona	201	7.7	37	1.4	52	2.0	34	1.3	324	12.4
Bilbao	161	5.9	42	1.5	48	1.8	59	2.2	310	11.4
Cartagena	280	10.4	32	1.2	42	1.6	34	1.3	388	14.4
Castellón	362	9.5	45	1.2	28	0.7	25	0.7	460	12.1
La Coruña	242	9.7	49	2.0	58	2.3	66	2.6	415	16.6
Madrid	159	6.5	28	1.1	64	2.6	58	2.4	309	12.7
Pamplona	184	7.2	30	1.2	26	1.0	12	0.5	252	9.8
San Sebastián	83	8.1	26	2.5	18	1.7	21	2.0	148	14.4
Valencia	342	11.6	43	1.5	56	1.9	45	1.5	486	16.5
Valladolid	282	10.7	44	1.7	29	1.1	25	0.9	380	14.4
Total	2482	8.6	429	1.5	468	1.6	419	1.5	3798	13.2

AE: atopic eczema, A: asthma, R: rinitis, Prev: prevalence.

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Table 3. Demographic, environmental characteristics and acetaminophen use.

	AE		AE+A		AE+R		AE+A+R		Total AE I	
	N	% 95% CI	N	% 95% CI	N	% 95% CI	N	% 95% CI	N	% 95% CI
Gender										
Male	926	37.3 35.4-39.2	204	47.6 42.9-52.3	188	40.3 35.9-44.8	206	49.2 44.4-53.9	1524	40.1 38.6-41.7
Age										
13	1256	50.6 48.7-52.6	211	49.2 44.5-53.9	246	52.6 48.0-57.1	218	52.0 47.2-56.81	1931	50.9 49.3-52.4
14	1225	49.4 47.4-51.3	218	50.8 46.1-55.5	222	47.4 42.9-52.0	201	48.0 43.2-52.8	1866	49.1 47.5-50.7
Acetaminophen use (last year)										
Never	237	12.4 10.99-13.94	26	7.3 4.96-10.43	45	11.0 8.24-14.32	11	2.9 1.54-5.00	319	10.5 9.4-11.6
1 /year	978	51.2 48.96-53.44	169	47.7 42.57-52.95	191	46.7 41.90-51.55	157	41.5 36.64-46.56	1495	49.0 47.2-50.8
1/month	695	36.4 34.25-38.57	159	44.9 39.79-50.13	173	42.3 37.57-47.13	210	55.6 50.51-60.51	1237	40.5 38.8-42.3
Mother's level of educational										
No qualifications	675	28.8 27.01-30.72	96	24.8 20.69-29.29	81	18.7 15.21-22.54	74	19.1 15.39-23.21	926	26.1 24.7-27.5
Primary	408	17.4 15.93-19.01	58	15.0 11.69-18.81	73	16.8 13.52-20.56	66	17.0 13.51-21.00	605	17.1 15.8-18.3
Intermediate	685	29.3 27.44-31.13	116	30.0 25.56-34.68	144	33.2 28.87-37.72	125	32.2 27.71-36.99	1070	30.1 28.6-31.7
University	573	24.5 22.77-26.25	117	30.2 25.81-34.95	136	31.3 27.10-35.82	123	31.7 27.21-36.46	949	26.7 25.3-28.2
Parental smoking										
No	795	41.7 39.49-43.91	131	37.5 32.57-42.71	157	38.2 33.59-42.97	146	39.0 34.19-44.06	1229	40.4 38.7-42.2
Yes	1112	58.3 56.09-60.51	218	62.5 57.29-67.43	254	61.8 57.03-66.41	228	61.0 55.94-65.81	1812	59.6 57.8-61.3

AE: atopic eczema, A: asthma, R: rinitis, N: Number, CI: Confidence Interval.

Table 4. Prevalence and Odds Ratios for diagnosed AE according to current acetaminophen use

Frequency of use	Prev	cPR	aPR	95% CI
AE				
Never	6.4	1.00	1.00	-
At least once a year	8.3	1.33	1.34	1.15-1.56
At least once a month	10.6	1.73	1.81	1.54-2.12
AE+Asthma				
Never	0.7	1.00	1.00	-
At least once a year	1.4	2.06	1.74	1.15-2.65
At least once a month	2.4	3.50	3.03	1.99-4.62
AE+Rhinitis				
Never	1.2	1.00	1.00	-
At least once a year	1.6	1.34	1.27	0.91-1.79
At least once a month	2.6	2.19	2.20	1.56-3.09
AE+Asthma+Rhinitis				
Never	0.3	1.00	1.00	-
At least once a year	1.3	4.54	4.05	2.19-7.49
At least once a month	3.2	11.05	10.08	5.48-18.55
total AE				
Never	8.6	1.00	1.00	-
At least once a year	12.7	1.55	1.51	1.32-1.72
At least once a month	18.8	2.45	2.49	2.17-2.85

Prev: prevalence, cPR: crude prevalence ratio, aPR: adjusted prevalence ratio for age, gender, parental smoker, mother's level of education, CI: Confidence Interval

DISCUSSION

The Spanish ISAAC phase 3 studies, performed among 13- to 14-year-old adolescents, provide self-reported prevalences of AE, asthma and rhinitis in a nationwide sample. The data reveal considerable variation in the prevalences of AE, asthma and rhinitis with increasing use of acetaminophen. This association is in agreement with findings from previous studies.^{28,30}

In our study, we find greater AE prevalence among adolescents whose mother has a high level of education, and the rates of AE, asthma and rhinitis appear to be very low among those whose mothers have a very low level of education. We attribute this to mothers with a lower level of education being less effective at detecting possible symptoms of AE.

Notably, variation with use of acetaminophen in the prevalence of current rhinitis or AE was less than variation in the prevalence of asthma or the combination of AE, asthma and rhinitis, especially if the drug had been used in the previous month.

Several mechanisms of action of acetaminophen

have been proposed,³¹ including depletion of glutathione and glutathione-dependent enzymes in airways. The increased risk of rhinitis and eczema suggests that the effect of acetaminophen is not restricted to airways.

We found an association between current acetaminophen use and current rhinitis and eczema symptoms in 13- to 14-year-old adolescents, and that this was independent of the presence of asthma. These observations suggest that acetaminophen may have systemic inflammatory effects, possibly by increasing oxidative stress resulting from the depletion of glutathione-dependent enzymes, which may also lead to enhanced Th2 allergic immune responses.^{12,13,27} Acetaminophen may suppress the immune response and prolong symptoms of rhinovirus infections,³² which are a common cause of severe exacerbations of asthma.³³⁻³⁵ Similarly, a recent study of prophylactic acetaminophen administered at the time of vaccinations has demonstrated that acetaminophen in routine antipyretic doses is capable of modulating immune responses.³⁶

On the other hand, we found no significant correlation between parental smoking and the prevalence of current AE, rhinitis and asthma in school children of primary education in Spanish cities.³⁷ Indeed, although environmental tobacco smoke is one of the most important indoor pollutants and has been postulated as a risk factor of childhood asthma and allergy,³⁸ the effects of parental smoking have been found to be inconsistent.⁹ In this study, once again we found no correlation between parental smoking and the prevalence of the three allergic symptom groups addressed herein.

This study has several strong points. The data were collected almost at the same time across the eleven geographical regions, with an internationally identical methodology used in all cases. Specifically, recognition of symptoms of AE, asthma and rhinitis in adolescents was based on validated symptom-based written questionnaires.²⁹ We used self-reported symptoms rather than diagnoses of medical professionals to avoid major diagnostic differences relating to access to medical care, language and medical practices among regions.

However, one weakness of the study could be that the information on symptoms was based on retrospective questionnaires, which could be subject to recall bias. However, we believe that symptom recall over the past 12 months provides a more accurate estimate of prevalence than the diagnostic labeling of diseases in our type of study. Finally, we considered only a limited range of potential confounders. Others, including family history of asthma and allergic diseases, history of infectious disease, diet, exercise and environmental pollution, should be considered in future research works.

In conclusion, the findings of our study are additional evidence indicating that acetaminophen use before adulthood may be associated with an increased prevalence of allergic diseases. However, it is not possible in a study of this design to determine whether a positive association observed is causal or not. We have to also take into account that allergic diseases such as eczema and asthma are multifactorial diseases. Consequently, 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 during pregnancy and adult life.

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