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Asthma attributable to atopy: does it depend on the allergen supply?

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The use of the population attributable fraction (PAF) of asthma owing to atopy has not been widely used in epidemiological studies on childhood asthma, especially to compare regions of the same country. The present study includes 1039 children from Cartagena, Spain (Mediterranean coast) and 663 from Madrid (centre of Spanish plateau) using the ISAAC phase II methodology (questionnaire and prick test to the most common allergens). While there were no differences in asthma symptoms between school children (aged 10–11 yr) from Madrid and Cartagena, atopy to any allergen was significantly higher in those from Madrid (40.9% vs. 29.3%, respectively, $p < 0.0001$). However, children from Madrid were mainly positive to pollen allergy whereas those from Cartagena were positive for mite allergy. PAF of all the different asthma symptoms owing to atopy (any positive skin test) and PAF of current wheezing owing to a more severe atopy (three positive wheals) were higher in children from Cartagena than those from Madrid (45.5% vs. 28.6% and 14.2% vs. 6.2%, respectively). Per cent of previous year wheezing attributable to atopy to specific allergens varied among those cities and was higher for *D. pteronissinus*, *D. farinae*, cat, and olive tree in children from Cartagena, and – conversely – higher for mixed grasses, mixed trees and *Alternaria* in those from Madrid. All of these differences remained significant even after adjusting for risk factors. PAF for asthma owing to atopy could be very different within the same country, probably depending on the allergen supply which may depend on environmental factors such as the climate.

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The prevalence of atopy (positive skin prick test) in children with current asthma symptoms varies worldwide; while in developed countries it is relatively similar, 62.4% in Spain (1), 58% in Sweden (2) and 69% in western Germany (3); data from developing countries show a considerable variability, e.g. 21.5% in Peru (4), 26% in Estonia (2) and 89% in Costa Rica (5). In those children without current asthma symptoms, the prevalence of atopy also varies, e.g. 28.7% in Spain, 31.4% in Peru, 22% in Sweden, 9% in Estonia and 65.5% in Costa Rica (1–5). This wide variability in the proportion of atopy observed in adolescents with current wheezing and also in those without it, would support the idea that atopy may just be a parallel event in the pathogenesis of asthma (6) and that the overestimation of atopy as a cause of asthma may have delayed the research on other important possible etiological mechanisms for the development of this disease (7).

Recently, this doubt on the real causal role of atopy in asthma has been illustrated by Pearce et al. (7), who analysing nine population-based surveys (n = 15,983 children) and using the population attributable fraction (PAF) demonstrated that only 54% of asthma cases were attributable to atopy (positive skin prick test). A large survey (8) carried out in England in adolescents and young adults demonstrated that PAF of current wheezing as a result of atopy (house dust mite specific immunoglobulin

E > 0.3 kU/l) was only 35%. Nevertheless, the use of PAF has not been widely employed in epidemiological studies on childhood asthma, although it is a concept that could add a very interesting perspective on the impact of asthma and offers a way of comparing studies in different populations worldwide.

The 'International Study of Asthma and Allergies in Childhood' (ISAAC) has provided a common methodology for epidemiological studies in children allowing a better comparison of the results (9). Using ISAAC phase II methodology in Australia, Ponsonby et al. (10) reported that the PAF fluctuates according to the severity of asthma, e.g. 75% for more than 12 wheezing episodes during the previous year vs. only 33% for asthma ever.

The prevalence of asthma in Spain is lower than that in the English-speaking countries with a similar socio-economic level (e.g. 7.8% in Spain vs. 18.4% in New Zealand) (9). Furthermore, Spain has two different climates owing to its geography: a mild and humid coastal climate (especially on the Mediterranean coast) and an extreme and dry plateau one (in the centre of the peninsula). In 1995 and 2002, the ISAAC phase I and III surveys carried out respectively in 9 and 11 different Spanish centres found that asthma prevalence was much higher in the coastal centres (11, 12). There is considerable evidence suggesting that climate change has an impact on the type and concentration of aeroallergens (13) and also on the prevalence of asthma (14). To the best of our knowledge, no study has yet compared the PAF of asthma as a result of atopy in different geographic/climate regions of the same country using ISAAC phase II methodology. This study was undertaken to compare the PAF of asthma as a result of atopy in two different climates in Spain (Cartagena with a mild and humid coastal – Mediterranean climate and Madrid which has an extreme and dry – continental – one).

Materials and methods

Population

A survey according to the ISAAC phase II protocol was performed in Cartagena and Madrid. This protocol includes a questionnaire of symptoms and risk factors together with a set of skin prick tests given to a large sample of school children 10–11 yr of age. In each city, a random sample of school children was invited to participate. The study population for Cartagena (n = 2637) was all children of that age attending school in the city district, and for Madrid (n = 2740) it was all the children of that age attending schools within the 'Hospital 12 de Octubre' health area. For the purpose of the present study, only the children with both the questionnaire and a valid skin prick test (positive wheal ≥3 mm) were included.

Questionnaire

A complete questionnaire according to ISAAC phase II was used to assess respiratory symptoms and risk factors (15). The six questions related to asthma symptoms were: (i) Has your child ever had wheezing or whistling in the chest at any time in the past? (ii) Has your child had wheezing or whistling in the chest during the last 12 months? (iii) How many attacks of wheeze has your child had during the last 12 months? (none, 1–3, 4–12, more than 12). (iv) In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing? (never, less than one night per week, one or more nights per week). (v) In the last 12 months, has wheezing been severe enough to limit your child's speech to only one or two words at a time between breaths? (vi) Has your child ever had asthma?

Other factors considered important for the study and included in the questionnaire were: gender, birth weight, breast feeding, older or younger siblings, attending nursery school prior to the age of 24 months, asthma, rhinitis or eczema in the mother and father, presence of a cat or a dog during the first year of the child's life, maternal smoking during pregnancy, living in a rural area and having mould stains on the household walls.

Skin prick test and definition of atopy

Skin prick tests were performed according to the ISAAC phase II protocol in the school setting. The extracts of allergen tested (ALK-Abello, Denmark) were: *Dermatophagoides pteronissimus*, *Dermatophagoides farinae*, cat, *Alternaria*, mixed trees (*Betula*, *Alnus* and *Corylus*), mixed grasses (*Dactylis*, *Lolium*, *Festuca*, *Poa*, *Phelum* and *Avena*) and positive (histamine 10 mg/ml) and negative controls. Two frequent regional allergens (olive tree and *Parietaria*) (ALK-Abello, Spain) were also included in the test. ALK-Abello (Denmark) lancets were used for the prick test. Fieldworkers were trained to obtain a maximum coefficient of variability of 20% using the histamine solution. When a child had a response to histamine of < 3 mm (maximum wheal diameter), he/she was considered as a non-responder and was excluded from the analysis. Skin prick test-positive subjects were defined as those who had at least one positive reaction (wheal diameter measuring 3 mm or more after subtraction of the control value). A child was defined as atopic when he/she had at least one positive skin prick test, otherwise he/she was considered as non-atopic.

Ethical approval

The study was approved by the ethics committee of the 'Hospital 12 de Octubre' (Madrid). Parents were asked to participate by answering the questionnaire and giving authorization to perform the prick tests on their children. A written explanation of the test procedure was included in the contact and authorization sheet.

Statistical analysis

Chi-square tests were conducted to identify which risk/protective factors had a statistically different ($p < 0.05$) prevalence in Cartagena as compared with Madrid. Those factors were later used for adjusting odds ratios (OR) and PAF. The prevalence of the different asthma symptom questions were compared between cities and the results were expressed in OR, Cartagena being the base (OR = 1). The proportion of asthma cases – as defined by the different questions – that were attributable to atopy in each city were estimated by the formula $P(\text{OR}-1)/\text{OR}$, where P is the proportion of cases that were exposed. PAF was also adjusted (aPAF) using the aOR in the aforementioned formula (7). Statistical calculations were carried out using the Stata 7.0 package software (Stata Corporation, College Station, Texas, USA).

Results

Of an initial 1471 children in Cartagena and 981 children in Madrid who completed the questionnaire, 1039 (70.6%) from Cartagena and 663 (67.6%) from Madrid had a complete data set (questionnaire and valid skin prick test). An appreciable number of parents (n = 427) from Cartagena and Madrid (n = 317) did not authorize performing a prick test on their children. However, the prevalence of previous year wheezing amongst those children who did not have the prick test but answered the questionnaire was not significantly different to the prevalence amongst those children who underwent the prick test (11.9% vs. 11.4% in Cartagena and 16.7% vs. 13.7% in Madrid, respectively). Additionally, five children from Cartagena and one child from Madrid were discarded because they did not react to histamine (non-responders).

Among the demographic characteristics, children from Madrid had a significantly higher percentage of low birth weight cases (less than 2500 g), a higher prevalence of maternal smoking during pregnancy and had more cats or dogs during their first year of life, than children from Cartagena. Conversely, significantly more children in Cartagena lived in a rural area, had younger siblings and went to a nursery school before the age of 2 y (Table 1). The prevalence of all asthma symptoms was higher in Madrid than in Cartagena, especially of those symptoms reflecting disease severity, e.g. more than 12 wheezing attacks, more than one night/week sleep disturbances by wheezing and speech-limiting wheeze last year. However, only the latter reached statistical significance (Table 2). Similarly, the prevalence of atopy was significantly higher among the children from Madrid than among those from Cartagena (40.9% vs. 29.3%, $p < 0.0001$), and this was also true for most of the different specific allergens tested (e.g. cat, *Alternaria*, mixed grasses, *Parietaria*, mixed trees and olive tree). The only specific allergens that were significantly more prevalent in Cartagena than in Madrid were *D. pteronissinus* and *D. farinae* (Table 3).

Table 1. Demographic characteristics and risk factors in children from Cartagena and Madrid (%)

	Cartagena (n = 1039)	Madrid (n = 663)
Male gender	51.0	47.8
Birth weight <2500 g*	8.7	14.0
Breast feeding for 6 or more months	68.7	65.5
Have older siblings	53.5	48.7
Have younger siblings*	47.1	40.7
Attended a nursery school before the age of 2 yr†	74.8	51.9
Mother suffers from:		
Asthma	7.8	8.7
Rhinitis	14.0	13.9
Eczema	15.4	19.3
Father suffers from:		
Asthma	5.4	4.7
Rhinitis	9.4	8.3
Eczema	9.4	9.2
Dog during the first year of life*	12.1	17.6
Cat during the first year of life*	4.6	8.1
Mother smoked during pregnancy*	23.1	30.1
Mould stains on the household walls‡	2.9	5.2
Live in a rural area†	17.6	4.5

*$p \leq 0.01$.
†$p \leq 0.001$.
‡$p < 0.05$.

Table 2. Percentage (95% confidence interval) of different asthma-related symptoms in children from Cartagena and Madrid

	Cartagena	Madrid	OR
Wheezing ever	30.7 (27.9–33.6)	31.8 (28.3–35.5)	1.05 (0.85–1.29)
Wheezing last year	11.4 (9.5–13.4)	13.7 (11.2–16.6)	1.24 (0.92–1.66)
Wheezing attacks last year			
1 to 3	8.8 (7.2–10.7)	9.1 (7.0–11.5)	1.07 (0.76–1.52)
4 to 12	1.8 (1.1–2.8)	2.7 (1.6–4.2)	1.61 (0.83–3.12)
>12	0.4 (0.1–0.9)	1.2 (0.5–2.3)	3.22 (0.96–10.76)
Sleep disturbances by wheezing last year			
<1 night/week	5.4 (4.1–6.9)	5.7 (4.1–7.7)	1.17 (0.76–1.81)
>1 night/week	1.1 (0.6–2.0)	2.1 (1.1–3.5)	2.04 (0.92–4.55)
Speech-limiting wheeze last year	1.6 (0.9–2.6)	3.2 (1.9–4.8)	1.97 (1.03–3.76)*
Asthma ever	9.5 (7.8–11.5)	11.3 (9.0–14.0)	1.21 (0.88–1.66)

*p = 0.055 between cities.
OR, odds ratio comparing the two cities, Cartagena being the base (OR = 1).

Table 3. Percentage (95% confidence interval) of positive skin prick test to the different allergens among children from Cartagena and Madrid

Positive skin prick test	Cartagena	Madrid	OR
Any positive test	29.3 (26.5–32.1)	40.9 (37.1–44.7)	1.67 (1.35–2.06)*
D. pteronissinus	20.6 (18.2–23.2)	11.8 (9.4–14.5)	0.51 (0.38–0.68)†
D. faringe	10.5 (8.7–12.5)	6.3 (4.6–8.5)	0.57 (0.39–0.84)*
Cat	7.8 (6.2–9.6)	15.2 (12.6–18.2)	2.12 (1.54–2.93)*
Alternaria	1.5 (0.9–2.5)	5.1 (3.6–7.1)	3.46 (1.84–6.76)*
Mixed grasses	3.0 (2.0–4.2)	25.5 (22.2–29.0)	11.12 (7.41–17.11)*
Parietaria	1.35 (0.7–2.2)	5.43 (3.8–7.4)	4.20 (2.19–8.50)*
Mixed trees	1.5 (0.9–2.5)	6.5 (4.7–8.6)	4.43 (2.42–8.50)*
Olive tree	8.37 (6.8–10.2)	15.7 (13.0–18.7)	2.03 (1.49–2.79)*
Mites positivity only	20.4 (17.9–22.8)	7.7 (5.6–9.7)	0.32 (0.23–0.45)*
Pollen positivity only	2.4 (1.7–3.3)	21.6 (18.5–25.0)	11.15 (7.13–18.02)*

*p < 0.0001 between cities.
†p < 0.01 between cities.
OR, odds ratio comparing the two cities, Cartagena being the base (OR = 1).

However, the PAF of the different asthma symptoms as a result of atopy was higher in Cartagena than in Madrid (Table 4). Those differences remained significant even after being adjusted (aPAF) for risk/protective factors that were significantly different between cities in the univariate analysis (birth weight < 2500 g, having younger siblings, attending a nursery school, having a dog or cat during the first year, maternal smoking during pregnancy, mould stains on the household walls and living rural area). For example, the PAF for wheezing in the previous year was 45.5% in Cartagena and 28.6% in Madrid, and their aPAF were 49.6% and 26.9%, respectively.

Similarly, when a more severe definition of atopy is used – e.g. three positive wheals in the skin test – the PAF and aPAF of wheezing in the previous year were also higher in children from Cartagena than from Madrid (PAF was 14.2% in Cartagena and 6.2% in Madrid, and their aPAF

Table 4. Population attributable fraction (PAF) of different asthma symptoms because of atopy (any positive wheal) in children from Cartagena and Madrid

	Cartagena		Madrid	
	PAF	aPAF	PAF	aPAF
Wheezing ever	26.2	25.2	20.6	13.9
Wheezing last year	45.5	49.6	28.6	26.9
Wheezing attacks last year				
1–3	36.0	40.6	22.9	27.6
4–12	85.1	81.7	54.9	43.0
>12	NA	NA	NA	NA
Sleep disturbances by wheezing last year				
<1 night/week	48.4	48.9	27.3	11.7
>1 night/week	39.1	48.1	42.0	NA
Speech-limiting wheeze last year	58.8	58.2	44.4	36.2
Asthma ever	45.3	46.9	39.7	23.2

aPAF, PAF adjusted by birth weight <2500 g, having younger siblings, attending a nursery school, having a dog or cat during the first year of the child's life, maternal smoking during pregnancy, mould stains on the household walls and living in a rural area.
NA, not available, as no calculation was possible owing to the small number of children.

Table 5. Population attributable fraction (PAF) of last year wheezing owing to atopy (based on the number of positive tests and the specific allergen) in Cartagena and Madrid

Positive skin prick tests	Cartagena				Madrid			
	OR	PAF	aOR	aPAF	OR	PAF	aOR	aPAF
Number of positives								
1+	1.2	2.4	1.0	0	0.8	0	1.9	6.2
2+	3.8	18.1	4.9	19.6	1.6	6.3	0.2	0
3+	8.6	14.2	16.1	15.1	2.0	6.2	3.7	8.8
Allergens								
Any positive test	4.3	45.5	6.1	49.6	2.0	28.6	1.9	26.5
D. Pteronissinus	4.0	34.4	5.9	38.0	1.7	7.6	1.8	7.8
D. Faringe	3.1	22.3	7.0	28.3	3.1	9.7	3.1	9.7
Mixed grasses	1.1	0.5	1.1	0.5	2.6	26.0	2.4	24.9
Mixed trees	2.7	2.1	6.3	2.8	1.7	4.1	3.5	7.1
Alternaria	3.7	3.1	7.0	3.6	3.8	9.7	7.6	11.5
Cat	3.8	15.1	7.2	17.5	1.4	6.2	1.4	5.1
Olive tree	2.6	10.4	3.6	12.3	1.6	8.5	2.1	11.5
Parietaria	NA	NA	NA	NA	2.6	6.7	8.2	9.7

aPAF, adjusted by birth weight <2500 g, having younger siblings, attending a nursery school, having a dog or cat during first year, maternal smoking during pregnancy, moulds stains and living rural area.
NA, not available, as no calculation was possible owing to the small number of children; OR, odds ratio; aOR, adjusted odds ratio.

15.1% and 8.8%, respectively) (Table 5). Curiously, when specific allergens were used for calculating PAF and aPAF of wheezing in the previous year, then those were higher in Cartagena for *D. pteronissinus*, *D. farinae*, cat and olive tree. Conversely, children from Madrid had higher PAF and aPAF for mixed grasses, mixed trees and *Alternaria* (Table 5). There were too few children from Cartagena with four or more positive wheals or positive to *Parietaria* to perform reliable calculations of OR and aOR.

Discussion

This study, using the ISAAC phase II protocol, shows that the PAF of all the different asthma symptoms as a result of atopy (any positive skin test) was higher in children from Cartagena (45.5%) than from Madrid (28.6%). Furthermore, the PAF of the previous year wheezing owing to a more severe atopy (three positive wheals) was higher amongst children from Cartagena than for Madrid (14.2% vs. 6.2%, respectively). Curiously, the PAF of current wheezing attributable to atopy based on specific skin prick tests varied between the two cities and it was higher for *D. pteronissinus*, *D. farinae*, cat, and olive tree in Cartagena, and –conversely – it was higher for mixed grasses, mixed trees and *Alternaria* in Madrid. All of these differences remained statistically significantly even after being adjusted for risk factors (aPAF).

In spite of the prevalence of most of the asthma symptoms being similar amongst children from Madrid and Cartagena, the prevalence of atopy – as measured by at least one positive wheal in the prick test – was significantly higher in the former city than in the latter (40.9% vs. 29.3%, $p < 0.0001$). However, children from Madrid were mainly positive to pollen whereas those from Cartagena were positive to mite allergy. These differences in specific allergens between cities could be expected owing to their differences in climate. Madrid is a city in the centre of the Spanish plateau with extreme and dry (continental) climate whereas Cartagena is a Mediterranean coast city with mild and humid climate. Therefore, having a similar prevalence of asthma and a different prevalence of specific atopy in two cities within the same country, it is interesting to know to what extent asthma symptoms are attributable to atopy (PAF) in each city. Surprisingly, children from Madrid had a lower PAF for asthma symptoms owing to atopy and severe atopy than did children from Cartagena. However, the PAF for pollens was higher in Madrid and the PAF for mites was higher in Cartagena, indicating that the characteristics of atopy in Madrid makes it less ‘asthmogenic’ for children than in Cartagena. Some studies support the idea that allergy to pollens is a poor risk factor for asthma compared with mites (16): even when atopy was much more frequent in Madrid, the fact that it is mainly because of pollen, makes asthma less prevalent.

Furthermore, it is interesting that although the number of children owning cats was double in Madrid than in Cartagena and the number who were sensitized to that specific allergen was also double, the PAF of wheezing in the previous year attributable to cats in Cartagena is triple than in Madrid. This fact probably indicates that the protection or risk of suffering from allergy/asthma when living with a cat at home could be dependent on additional environmental or climate factors, such as heating systems, contact with other allergens and the like. It should be underlined that not every possible risk or protective factor was controlled in the present study. Thus, it is possible that other factors different from the allergen supply could be modifying the relationship between atopy and asthma within the two studied populations. For example, it is possible that the different prevalence of helminth infestation between the two cities could modulate the association between asthma and atopy differently (17). Furthermore, the exposition of children to endotoxins, which also influences the relationship between asthma and atopy – and that should be measured by the endotoxin levels on the children's mattresses (18) – could be different between the two studied cities.

Nonetheless, in recent years, some studies have shown the impact of climate on aeroallergens: pollen amount, allergenicity, seasonality and distribution; and to a less extent on other allergens such as mould spores, house dust mites and cockroaches (13). Moreover, it has been hypothesized that the anthropogenic climate change might be a plausible contributor to the increase in asthma incidence, prevalence and morbidity over recent decades (14). However, the long-term effects of climate on asthma have been very rarely considered and deserve more attention (19).

Pearce et al. (7) reported a broad range of PAF of asthma as a result of atopy (at least one positive skin test) in children, using some epidemiological studies, and suggested that the PAF may depend on the age groups, asthma definition, climate and/or other environmental factors. For example, a PAF of 25% was calculated amongst children 12–14 yr old from Los Alamos, New Mexico (altitude 2220 m and semi-arid, continental climate) (20); this number was quite similar to the 27% obtained in Leipzig and Halle, former East Germany (Leipzig altitude 120 m and Halle altitude 280 m, both with a continental climate), amongst children of 9–12 yr old (21) and the 28.6% obtained in Madrid (altitude 650 m, continental climate and a full 'westernized' population) in the present study. Furthermore, a PAF of 32% was calculated among children aged 6 yr from Tucson (altitude 792 m and desert climate) (22). On the other hand, higher PAF have been reported in areas of more humid and less extreme climate. For example, a PAF of 40% was reported amongst children aged 14 from Umea, Sweden (altitude 26 m and Atlantic climate) (23), 38% amongst children 4–9 yr old in Leicester, UK (altitude 96 m and Atlantic climate) (24) and 57% amongst children 7–12 yr from Kuopio, Finland (altitude 100 m and sub-Arctic climate) (25). In the present study, a PAF of 45.5% was found in children from Cartagena (sea-level city with a Mediterranean climate). There is at least one exception to this trend of extreme and dry climates related to lower asthma PAF as a result of atopy and this is Munich where a PAF of 51% was reported (altitude 500 m and continental climate) (21). However, Munich is more humid than Madrid.

In summary, we have shown how different the fraction of asthma attributable to atopy could be within the same country, probably depending on the different allergen supply (although the impact of other factors, such as the exposition to endotoxins or the infestation by helminths, could not be entirely ruled out), which is mainly dependent on the local climate. Even when atopy was more prevalent in Madrid (an extreme and dry plateau city) than in Cartagena (a mild and humid coastal city), the PAF as a result of atopy was higher in Cartagena. Furthermore, PAF due to particular allergens differed between cities.

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