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A different pattern of risk factors for atopic and non-atopic wheezing in 9–12-year-old children

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Few epidemiological studies have compared the risk factors of asthma or wheezing between atopic and non-atopic children. The objective of this study was to determine if there are specific risk factors for current wheezing related to atopic status in schoolchildren. Schoolchildren 9–12 yr of age from three Spanish cities (n = 2720) were subject to a cross-sectional study of asthma risk factors (by questionnaire) and atopy (by skin prick test) according to the ISAAC phase-II protocol. Risk factors for current wheezing (in the last 12 months) as reported by parents were investigated among the atopic (positive prick test to at least one allergen) and the non-atopic (negative prick test) children. The prevalence of current wheezing was 13.1% in the whole group, 22.1% in the atopic group and 7.8% in the non-atopic group. However, only 62.4% of children with current wheezing were atopic. Male gender and asthma in the mother and/or the father were both significant and independent risk factors for current atopic wheezing, whereas maternal smoking in the first year of the child's life and mould stains on the household walls were for current non-atopic wheezing. In summary, this study shows that atopic and current non-atopic wheezing children in Spain do not share identical environmental and family risk factors.

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The existence of several asthma phenotypes during childhood has been hypothesized based on data from cohort studies (1, 2). At the age of 9–12 yr two main asthma phenotypes could be coexisting: non-atopic wheeze and IgE-associated wheeze/asthma (1). Elevated IgE has been shown to correlate with asthma symptoms or doctor diagnosed asthma even in the absence of atopy (defined by skin prick testing) leading to the idea that 'real asthma' has almost invariably an allergic basis both in children (3) and in adults (4). By the age of 14 yr most asthma cases seem to be related to IgE (1, 5). However, Pearce et al. (6) in an analysis of nine population based surveys in children showed that only 58% of asthmatics were atopic (skin prick test positive) and suggested that the importance of atopy as a cause of asthma may have been overestimated. Moreover, a very large survey (7) carried out in a population of 11–29-year old showed that the proportion of recent wheeze attributable to atopy was only 35%. The authors emphasized the fact that with the same respiratory symptoms the atopic subject was more prone to label his/her disease as asthma than the non-atopic one was. However, the importance of atopy as a risk factor for asthma should not be underestimated: atopy is the main risk factor for the persistence (1) and severity of wheezing (8, 9).

Only relatively few studies have investigated whether or not children with atopic and non-atopic asthma have different risk factors for active wheezing. In Sweden (10) a study performed among children 7–8-year old demonstrated that male gender, dampness in the home,

maternal smoking and less than 3 months breast feeding were risk factors among non-atopic asthmatics; in contrast having a pet at home was a protective factor for atopic asthmatic children. A survey of asthmatics 20–44-year old in Albania (11) reported that maternal asthma was a risk factor among atopic asthmatics whereas maternal and personal smoking and having older siblings were risk factors among non-atopic asthmatics. Very recently Kurukulaartchy et al. (12) have shown in the Isle of Wight cohort study that male gender was a risk factor only among atopic individuals with wheeze, whereas recurrent chest infections at the age of 2 were associated only with non-atopic wheezing individuals.

Since the prevalence of asthma or wheezing in children is very different around the world (13), it is important to investigate potential differences in risk factors for atopic and non-atopic asthmatic/wheezing children in various countries.

The purpose of the present study is to evaluate environmental and family risk factors for atopic and non-atopic wheezing among schoolchildren in Spain using the International Study of Asthma and Allergies in Childhood (ISAAC) phase-II protocol.

Material and methods

The ISAAC phase-II protocol (14) was carried out in three Spanish cities: Cartagena, Madrid and Almería. All cities that participated in ISAAC phase I in Spain were invited to participate in phase II, but only the previously mentioned cities were able to carry out the whole protocol. Cartagena and Almería are two cities on the southeast Mediterranean coast of Spain of about 150,000 inhabitants each, in a region that has grown greatly during the last decade; both live on mainly tourism and services. In Cartagena and Almería the eligible children were those in fifth grade (9–12-year old) in schools within the city district; in Madrid, where the fifth grade was also surveyed, the geographical area was the health district of the 'Hospital 12 de Octubre'. This district of the south of Madrid comprises a population of 700,000 and has a medium-low socioeconomic status. The study was approved by the ethics committee of the aforementioned hospital for all the three centres. Phase-II questionnaires translated into Spanish were sent to the parents of a random sample of schools in each city. 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.

For the purpose of this study, as has been the usual practice in the ISAAC study, a child was considered to suffer from current wheezing if the parents answered affirmatively to the question 'Has your child had wheezing or whistling in the chest during the last 12 months?'. A validation of the core question on current wheezing was made against a bronchial challenge test with hypertonic saline as explained below. A number of potential risk factors for current wheezing were examined: low birth weight (less than 2500 g); exclusive or non-exclusive breast feeding (any length of time); older or younger siblings (yes or no); attending nursery school prior to the age of 24 months (yes or no); asthma, rhinitis or eczema in the mother or father (yes or no); university studies of the mother (yes or no); and living in an urban or rural area. In addition the following information was obtained both at the time of the questionnaire as well as during the first year of the child's life: smoking habits of the mother; having a dog or a cat in the house; and having mould stains on the household walls. Furthermore, the questionnaire inquired about the type of fuel used for cooking and heating the house, together with the type of pillow, bedding and floor of the child's bedroom and the frequency of intake of the following foods: meat, fish, fresh fruit, raw green vegetables, cooked green vegetables, burgers, fruit juice and fizzy drinks.

Skin prick tests were performed according to the ISAAC phase-II standards in the school setting. The extracts of allergen tested (ALK-Abello) were: *Dermatophagoides pteronysinus; D. 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. ALK-Abello (Denmark) lancets were used for the prick test. When a child had a response to histamine of < 3 mm (maximum wheal diameter) he/she was considered a non-responder and was excluded from the analysis. Skin 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 was positive to one or more allergen in the skin prick test, otherwise he/she was considered as non-atopic.

In a subsample of children from one of the centres (Cartagena) a bronchial challenge test with hypertonic saline (4.5%) according to the ISAAC phase-II protocol (14) was performed. This subsample included 91 current non-wheezing and

67 current wheezing children. Sensitivity and specificity of the question used to define current wheezing was calculated against the result of the bronchial challenge test.

Separated univariate analyses were conducted to identify risk factors that were associated with either current atopic wheezing and with current non-atopic wheezing. Those factors that showed significance ($p < 0.05$) or near significance ($p \leq 0.1$) for current wheezing in the univariate analysis were included in a multivariate analysis. Two models of multivariate analyses were done: one including all factors with statistical significance and near significance in the univariate analysis (model 1) and another including only the significant ones (model 2). The size of the effect of each risk factor was measured by using the odds ratio (OR) and 95% confidence intervals (CI). When the same factor was measured at the time of the questionnaire and during the first year of the child's life (e.g. smoking habits of the mother, having a dog or a cat in the house and having mould stains on the household walls), the more significant of the two was incorporated to the multivariate analysis. Due to the association found between having an asthmatic father and an asthmatic mother the variable introduced in the multivariate analysis was 'having maternal and/or paternal asthma'. Adjusted OR (aOR) was calculated using a logistic regression model. Statistical calculations were carried out using the Stata 7.0 package software (Stata corporation, College Station, TX, USA).

Results

A total of 8052 children were invited to participate in the study and 3623 parents completed the questionnaire (participation rate 45%); 2848 of them (78.6%) received a skin prick test. The number of children with both a completed questionnaire and prick testing was 2788 (77%). The number of non-responders to the prick test was 68 consequently the total number of children with valid data for the study was 2720. There were no differences in prevalence for current wheezing and other demographic variables between the 68 children excluded and the remaining 2720 (data not shown). Among those 2720 children (mean age 10.1 ± 0.7 yr), 1718 (63.2%) were non-atopic and 1002 (36.8%) were atopic. The prevalence of current wheezing was 13.1% (356/2720) in the whole group, 22.1% (222/1002) among the atopic children and 7.8% (134/1718) among the non-atopic ones. The difference in the prevalence of wheezing among the atopic and the non-atopic children was statistically significant ($p < 0.001$). However, only 62.4% of children with current wheezing were atopic.

The sensitivity and specificity of the current wheezing definition compared to the result of the bronchial challenge test was 79.7% (95% CI: 78.7–80.1) and 79.8% (95% CI: 79.2–80.3), respectively.

The general characteristics of the whole population of children included in the analysis are shown in Table 1. Significant risk factors for current wheezing among the atopic children were male gender, maternal asthma and paternal asthma (Table 2). On the contrary, risk factors for current wheezing among the non-atopic children included maternal smoking (at the time of the questionnaire and in the first year of the child's life), maternal asthma and mould stains on the household walls at the time of the questionnaire (Table 3). The OR of having an asthmatic mother when having an asthmatic father was 2.12 (95% CI: 0.99–4.19) and 3.56 (95% CI: 1.88–6.42), respectively for atopic and for non-atopic children. For this reason, the composite variable 'asthma in the mother and/or the father' was used in the multivariate analysis.

No association was found between current wheezing and the different fuels used for cooking or heating the house, floor coverings or types of

Table 1. Overall characteristics of the whole population of children (n = 2720); n (%) except for age (mean ± s.d.)

Age	10.13 ± 0.7
Male gender	1344 (50.6)
Wheezing last year	356 (13.1)
Asthma diagnosis	316 (11.6)
Rhinitis symptoms last year	537 (19.7)
Eczema symptoms last year	288 (10.6)
Atopy	1002 (36.8)
Maternal asthma	233 (8.6)
Paternal asthma	147 (5.4)
Maternal rhinitis	390 (14.3)
Paternal rhinitis	255 (9.4)
Maternal eczema	456 (16.8)
Paternal eczema	269 (9.9)
Birth weight <2500	275 (10.1)
Breast feeding (any time)	1944 (71.5)
Younger siblings	1253 (46.1)
Older siblings	1411 (51.9)
Nursery school at <24 months	681 (25.0)
Current maternal smoking	1212 (44.6)
Maternal smoking first year	992 (36.5)
Maternal smoking during pregnancy	540 (19.9)
Mould stains currently	77 (2.8)
Mould stains first year	145 (5.3)
Rural area	607 (22.3)
University studies in mother	576 (21.3)
Dog ownership currently	607 (22.3)
Dog ownership first year	339 (12.5)
Cat ownership currently	247 (9.1)
Cat ownership first year	135 (5.0)

Table 2. Univariate analysis of risk factors for current wheezing among atopic children

	Atopic wheezing		Atopic non-wheezing				
	n	%	n	%	OR	95% CI	p Value
Male gender	143/222	64.4	420/780	53.8	1.55	1.12–2.14	0.005
Maternal asthma	29/222	13.1	66/780	8.5	1.62	0.98–2.63	0.03
Paternal asthma	23/222	10.4	47/780	6.0	1.80	1.01–3.11	0.02
Maternal rhinitis	36/222	16.2	123/780	15.8	1.03	0.67–1.57	0.87
Paternal rhinitis	31/222	14.0	93/780	11.9	1.20	0.75–1.88	0.41
Maternal eczema	38/222	17.1	139/780	17.8	0.95	0.62–1.42	0.81
Paternal eczema	22/222	9.9	78/780	10.0	0.99	0.57–1.65	0.97
Birth weight <2500	23/215	10.7	78/761	10.2	1.05	0.61–1.74	0.85
Breast feeding (any time)	158/217	72.8	552/770	71.7	1.06	0.75–1.51	0.75
Younger siblings	99/222	44.6	351/780	45.0	0.98	0.72–1.34	0.91
Older siblings	116/222	52.3	388/780	49.7	1.10	0.81–1.51	0.51
Nursery school at <24 months	56/165	33.9	208/559	37.2	0.87	0.59–1.27	0.44
Current maternal smoking	102/210	48.6	338/739	45.7	1.12	0.81–1.54	0.47
Maternal smoking first year	83/195	42.6	270/683	39.5	1.13	0.81–1.58	0.44
Maternal smoking during pregnancy	41/188	21.8	152/670	22.7	0.79	0.63–1.42	0.79
Mould stains currently	10/215	4.7	20/764	2.6	1.81	0.74–4.1	0.12
Mould stains first year	17/196	8.7	38/713	5.3	1.69	0.87–3.14	0.08
Rural area	23/222	10.4	75/780	9.6	1.08	0.63–1.81	0.74
University studies in mother	44/222	19.8	168/780	21.5	0.90	0.60–1.32	0.58
Dog ownership currently	51/222	23.0	174/780	22.3	1.03	0.71–1.50	0.83
Dog ownership first year	35/222	15.8	90/780	11.5	1.43	0.91–2.22	0.09
Cat ownership currently	28/222	12.6	68/780	8.7	1.51	0.91–2.45	0.08
Cat ownership first year	11/222	5.0	38/780	4.9	1.01	0.46–2.07	0.96

OR, odds ratio; CI, confidence intervals.

Table 3. Univariate analysis of risk factors for current wheezing among non-atopic children

	Non-atopic wheezing		Non-atopic non-wheezing				
	n	%	n	%	OR	95%CI	p Value
Male gender	66/134	49.2	747/1584	47.2	1.09	0.75–1.57	0.64
Maternal asthma	17/134	12.7	121/1584	7.6	1.76	0.96–3.06	0.04
Paternal asthma	9/134	6.7	68/1584	4.3	1.60	0.68–3.33	0.19
Maternal rhinitis	21/134	15.7	210/1584	13.3	1.21	0.71–2.00	0.43
Paternal rhinitis	16/134	11.9	115/1584	7.3	1.73	0.92–3.05	0.05
Maternal eczema	21/134	15.7	258/1584	16.3	0.95	0.55–1.56	0.85
Paternal eczema	17/134	12.7	152/1584	9.6	1.37	0.75–2.36	0.25
Birth weight <2500	13/128	10.2	161/1528	10.5	0.96	0.48–1.75	0.89
Breast feeding (any time)	100/132	75.8	1134/1542	73.5	1.12	0.73–1.76	0.59
Younger siblings	71/134	53.0	732/1584	46.2	1.31	0.91–1.90	0.13
Older siblings	66/134	49.3	841/1584	53.1	0.86	0.59–1.24	0.39
Nursery school at <24 months	33/95	34.7	384/1129	34.0	0.88	0.64–1.63	0.88
Current maternal smoking	73/125	58.4	699/1488	47.0	1.58	1.08–2.34	0.01
Maternal smoking first year	62/113	54.9	577/1370	42.1	1.67	1.11–2.50	0.008
Maternal smoking during pregnancy	34/111	30.6	313/1350	23.2	1.46	0.93–2.27	0.07
Mould stains currently	8/129	6.2	39/1524	2.6	2.52	0.99–5.61	0.02
Mould stains first year	10/122	8.2	80/1410	5.7	1.48	0.67–2.97	0.255
Rural area	15/134	11.2	179/1584	11.3	0.99	0.52–1.74	0.97
University studies in mother	25/134	18.7	342/1584	21.6	0.83	0.51–1.32	0.43
Dog ownership currently	28/134	20.9	354/1584	22.3	0.91	0.57–1.43	0.69
Dog ownership first year	20/134	14.9	194/1584	12.2	1.25	0.72–2.09	0.37
Cat ownership currently	8/134	6.0	143/1584	9.0	0.64	0.26–1.33	0.23
Cat ownership first year	3/134	2.2	83/1584	5.2	0.41	0.08–1.28	0.12

OR, odds ratio; CI, confidence intervals.

pillow or bedding either among the atopic children or among the non-atopic ones (data not shown). Also, the frequency of intake of any individual food was not related to the prevalence of wheezing in either of the two groups (data not shown).

Table 4. Adjusted odds ratios for current wheezing among atopic and non-atopic children for those factors found significant or near significant (model 1) and significant (model 2) in the univariate analysis (Tables 1 and 2). Adjustment was made for all the factors in the table

	Model 1		Model 2	
	Non-atopic wheezing aOR (95% CI)	Atopic wheezing aOR (95% CI)	Non-atopic wheezing aOR (95% CI	Atopic wheezing aOR (95% CI
Male gender	1.15 (0.78–1.71)	1.56 (1.11–2.19)**	1.17 (0.79–1.73)	1.53 (1.09–2.14)**
Maternal or paternal asthma	1.39 (0.80–2.42)	2.10 (1.39–3.18)***	1.50 (0.88–2.56)	2.16 (1.44–3.22)***
Maternal smoking first year	1.74 (1.17–2.58)**	1.12 (0.80–1.56)	1.72 (1.16–2.55)***	1.15 (0.82–1.60)
Mould stains currently	2.66 (1.13-6.25)*	1.78 (0.78–4.10)	2.70 (1.16–6.30)**	1.86 (0.81–4.24)
Cat ownership currently	0.66 (0.31–1.41)	1.58 (0.94–2.67)		
Dog ownership first year	1.29 (0.75–2.23)	1.22 (0.75–1.96)		
Paternal rhinitis	1.45 (0.77–2.75)	1.05 (0.65–1.71)		

aOR, adjusted odds ratio; CI, confidence intervals.
*p < 0.05, **p < 0.01, ***p < 0.001.

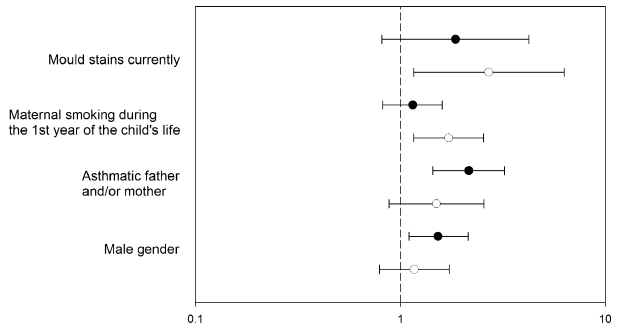

Fig. 1. Summary of risk factors for current wheezing among atopic (●) and non-atopic (○) children. The horizontal bars represent adjusted odds ratios together with the 95% confidence intervals.

In a multivariate analysis (either model 1 or 2), risk factors that remained significantly and independently associated with current wheezing at the time of the questionnaire among atopic children were male gender and paternal and/or maternal asthma; whereas among non-atopic children those factors were maternal smoking and current mould stains on the household walls (Table 4 and Fig. 1).

Discussion

A first interesting finding of this study is that only 62.4% of children of ages 9–12 yr with current wheezing were atopic in this sample. This percentage is similar to the one found in an assessment of nine population based surveys (6) and reinforces the idea that the importance of atopy as a cause of asthma may have been overestimated and overemphasized in children. This will be an important issue to consider when elucidating potential etiological mechanisms or prevention actions for the development of asthma in children. However, it is possible that if we had considered wheezing at any time in life this percentage would have been higher as the intervention on environmental or risk factors or antiasthmatic treatment could have reduced the prevalence of current wheeze among atopics.

The present study performed using a Spanish version of the ISAAC (a very well known international questionnaire for asthma in children) and the definition of current wheezing used here had a quite good sensitivity and specificity (both around 80%) when was tested against a positive bronchial challenge test with hypertonic saline. Ronmark et al. (10) also using the ISAAC questionnaire among Swedish children 7–8-year old, reported male gender, dampness at home, maternal smoking and breast feeding < 3 months as risk factors for non-atopic asthma. On the other hand, having pets at home was as a protective factor for atopic asthma. However, family history of asthma (not specifying father, mother or both) was a common risk factor for both atopic and non-atopic asthma. In our study the influence of family history of asthma is high both among atopic and non-atopic current wheezing children; however only in the case of the current atopic wheezing children was this influence independently significant. Similarly, a recent survey in adult asthmatic Albanians (20–44-year old) found maternal asthma as a risk factor only for atopic asthma (11).

Halonen et al. (15) in the Tucson Childrens' Respiratory Study described two asthma subphenotypes among children 6 yr of age according to their skin test reactivity to *Alternaria,* the most common aeroallergen (and the only allergen related to asthma) in this desert environment (16). This classification is not the same as the one used in the present study, as the *Alternaria*-negative children could have been positive to other allergens. They reported that male gender and maternal smoking had a similar effect

between the two *Alternaria* groups. However the *Alternaria*-negative asthma group had twice the frequency of lower respiratory tract infections in the first year of life and their asthma/wheezing symptoms more frequently remitted by the age of 11 than in the *Alternaria*-positive asthma group. More interestingly, *Alternaria*-positive asthma was influenced by maternal and paternal asthma, whereas in *Alternaria*-negative asthma only maternal influence was evident. The present study could not analyse maternal vs. paternal influences in the whole population due to a strong association between asthma in the father and in the mother.

We also found that the impact of maternal smoking in the first year of child's life on the current wheezing at the age of 9–12 yr differed between atopic and non-atopic children and constituted an independent and significant risk factor only among non-atopics, as was also reported by Ronmark et al. (10) and more recently by Priftanji et al. (11), but in contrast to the findings of Halonen et al. (15). It is quite possible that maternal smoking is not a determining factor of the asthma symptoms (as opposed to severity) among atopics, who have atopy as their main risk factor. It is noteworthy that the Isle of Wight study (12) did not find parental smoking to be a risk factor for non-atopic wheezing in the multivariate analysis. However the authors did find an association with non-atopic wheezing but not with atopic wheezing in their univariate analysis, and this association could have disappeared in the multivariate analysis due to interactions with other factors such as 'recurrent chest infections at 2 yr' (which was an independent risk factor only for non-atopic wheezing).

In the present study we found that current mould stains on the household walls (a marker of dampness) was an independent risk factor for wheezing only among non-atopics. Ronmark et al. (10) reported dampness as a risk factor among the same subpopulation. The relationship of dampness with recurrent infections during infancy remains to be elucidated (17, 18), but this relationship could be a possible explanation for this association, especially in the light of the results of the Isle of Wight study (12) in which recurrent chest infections at the age of 2 were associated only with non-atopic wheeze.

The study by Court et al. (7) in a national sample of English adults (including children from the age of 11) showed that male gender was a protective factor for wheezing in the atopic group (defined as a house dust mite specific IgE >0.3 kU/l), but not in the non-atopic group. In addition, those who came from lower social classes, lived in urban setting and were older had a significantly higher prevalence of wheezing among the non-atopics. In the present study male gender was an independent risk factor for wheezing only among atopics, as was also reported by the Isle of Wight study (12). However, in the present study neither living in a rural area nor having a mother with university studies were related to wheezing in any of the two groups. The distinct ages of the individuals of the two studies could explain the different results.

The limitations of this study are inherent in its design: there is a risk of recall bias because of the relatively remote nature of the antecedent events. Another possible limitation of the present study is the low participation rate (45%) in this ISAAC phase-II protocol: this participation rate cannot rule out the possibility of a self-selection of parents based of the interest found in the questionnaire (selection bias). However we do not consider that this low rate could have significantly biased the results of the study for three reasons. First, this is not a study on the prevalence of asthma or atopy. Second, there are a sufficient number of children to detect associations between the risk factors and the outcome variable. Final, and claiming caution when comparing a self-completed with a parent-completed questionnaire, a new survey (ISAAC phase-III protocol) in children 13–14-year old (self-completed questionnaire) carried out 1 yr after the present study (participation rate $>90\%$) yielded a very similar prevalence of current wheezing (12.7% for the pooled data from Cartagena and Madrid; this last survey was not performed in Almería, unpublished data from the authors).

In summary, in this study sample only around 60% of children 9–12-year old who have current wheezing were atopic. Also, children with atopic and non-atopic wheezing do not share identical environmental and family risk factors: male gender and asthma in the mother and/or father were independent risk factors for current wheezing among atopics, whereas maternal smoking in the first year of child's life and current mould stains on the household walls were for non-atopics wheezing.

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