

Risk factors for asthma in young adults

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ABSTRACT: We assessed the association of asthma prevalence in young adults with susceptibility factors and environmental exposures, taking into account the age at asthma onset.

A random sample of the general population, aged 20–44 yrs, in five areas of Spain (Albacete, Barcelona, Galdakao, Huelva, and Oviedo) was selected in the frame of the European Community Respiratory Health Survey (ECRHS). Overall, 2,646 subjects (response rate = 60.9%) responded to a respiratory questionnaire and 1,797 (41.4%) finalized a bronchial challenge.

Atopy to perennial (odds ratio (OR) = 10.2, 95% confidence interval 4.2–25) and seasonal allergens (11.5, 4.6–28), parental asthma (4.5, 2.5–8.4), and birth order (OR for no older siblings in comparison to having more than two = 3.2, 1.2–9.1) were associated with current asthma whatever the age of asthma onset. Past asthma was associated to a lesser extent with atopy (OR around 3.5 to both perennial and seasonal allergens). Lower respiratory tract infections before the age of 5 yrs (LRTI), having had a pet in childhood, and being born in a younger cohort were associated with asthma starting before the age of 15 yrs, but not after. Male gender was more frequent in childhood asthma and female gender in adulthood.

In addition to the known risk factors of asthma (atopy to perennial allergens, parental asthma) we provide evidence for an association of asthma (whatever the age of onset) with sensitization to seasonal allergens, and having less than three older siblings; and for an association of childhood asthma with lower respiratory tract infections.

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The role of many risk factors involved in the onset of asthma and exacerbation remains, in part, controversial. The production of specific immunoglobulin E (IgE) antibodies in response to environmental allergens (atopy) has been strongly associated with asthma [1]. Allergen exposure in sensitized children is known to initiate an immediate and late cellular airway reaction and bronchial obstruction [2]. However, though asthma is strongly associated with atopy, it only occurs in a proportion of atopics [3]. It is unclear to what extent asthma relates to the type of allergen (due to a different potency, such as the supposed supremacy of *Dermatophagoides pteronyssinus* [4, 5]) rather than to the level of allergen in the environment (as occurred in places without *D. pteronyssinus* [6]). In addition, viral infections in early life may protect [7] or, in contrast, enhance [8] the sensitization process. In adulthood, high exposures to new allergens, such as occupational allergens [9], may mimic the sensitization process occurring in early life. Other factors in adulthood, such as exposure to irritants [10] have been proposed as contributors to the persistence of asthma at that age.

Asthma is a chronic episodic disease initiated in childhood in many subjects [11]. Although the overall fea-

tures of asthma are similar in children and adults, there are numerous distinctions [12]. Thus, the study of risk factors involved in asthma onset and exacerbation requires a temporal perspective that only large follow-up studies can provide. A cheaper, but less valid approach is to use retrospective information provided by cross-sectional studies carried out in adulthood.

We assessed the association of susceptibility factors, environmental exposures in childhood and adulthood with asthma prevalence, at ages ranging 20–44 yrs, in a community-based sample in Spain, taking into account the age of asthma onset. The study forms part of the European Community Respiratory Health survey (ECRHS) [13]. Occupational exposures are not examined in this paper since they refer to specific segments of the population rather than to the general population. Exposures to irritants and maternal smoking were not assessed due to limits in the statistical power of the study.

Methods

A sample of 16,884 subjects, aged 20–44 yrs, was randomly selected from the general population of five areas in Spain (Albacete, Barcelona, Galdakao, Huelva,

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and Oviedo). A short and simple screening respiratory questionnaire was administered by mail and telephone to 85% of the subjects. In a second phase, a random subsample of 3,310 subjects from the original sample (~20%) was selected. In addition, 1,029 individuals (symptoms subsample) who reported "symptoms related with asthma" in the short respiratory interview, but who were not included in the random subsample, were also invited to take part in this second phase of the study. From March 1992 to April 1993, subjects were invited to attend a centre in each city. The ECRHS respiratory questionnaire [13] on respiratory symptoms and environmental risk factors was completed, in addition to a basic spirometry, a dose-response methacholine challenge test, and total and specific serum IgE responses to pets, pollen and mould levels. All the tests were performed during the same visit. From the 4,339 individuals, 2,646 (60.9%) responded to the ECRHS respiratory questionnaire on symptoms and risk factors and 1,797 (41.4%) completed a bronchial responsiveness challenge. Cases were derived from both the random and the symptoms subsamples. Controls were derived exclusively from the random subsample. Subjects from the symptoms subsample who did not correspond to the definition of a case were excluded. The Institutional Review Board of the participating centres approved the study protocol and patients gave written informed consent.

We classified asthma (that is a report of "ever having had asthma") according to the age of onset before or after 15 yrs of age. This cut-off point was based on clinical significance and also statistical criteria (since 15 yrs is the median age of onset in this population). Secondly, asthma was divided into current or past according to a report of an attack of asthma during the last 12 months. "Current asthma" could also be envisaged as a more specific definition since it appears strongly associated with concurrent measurements of pulmonary function or nonspecific airway responsiveness [14]. To increase the specificity in the definition [15] we used a second definition incorporating bronchial responsiveness. Subjects who reported ever having had asthma and showed bronchial hyperresponsiveness, were classified as cases.

Bronchial hyperresponsiveness was measured through a methacholine inhalation challenge test [13]. Bronchial responsiveness was defined as a fall in forced expiratory volume in one second (FEV₁) by $\geq 20\%$ of the value following saline inhalation at a maximum concentration of methacholine of 100 mg·mL⁻¹ (*i.e.*, 5.117 mmol) or extrapolated to 8 mmol. Thus, bronchial hyperresponsiveness was expressed as a dichotomous variable: presence or absence of a fall in FEV₁.

Atopy was assessed by means of serum-specific IgE response (capsulated hydrophilic carrier polymer (CAP) method) in a central lab and skin sensitivity tests following a standard procedure [13]. A subject was considered atopic if any of the responses to indoor allergens (cat dander, *Cladosporium*, *D. pteronyssinus*) and outdoor allergens (*Alternaria*, birch, olive, *Parietaria*, ragweed, timothy grass) were positive (*i.e.*, a skin response > 3 mm or a CAP > 0.35 kU·L⁻¹) [13]. Nonatopy was a negative response to all the antigens.

The association of asthma symptoms and bronchial hyperresponsiveness with the risk factors, was calcu-

lated by the odds ratio (OR) using standard methods of logistic regression analysis [16]. Subjects without symptoms of asthma or asthma and bronchial hyperresponsiveness were taken as the control group. Variables that modified the association of a given risk factor with asthma symptoms were estimated by testing the significance of interactions in the logistic regression model. A *p*-value of 0.05 was defined as representing statistical significance.

Results

The sociodemographic characteristics of subjects in the study according to the classifications used to define asthma (area, sex and age) is shown in table 1. Participants in the bronchial challenge test differed significantly for area and sex compared to those who were only interviewed.

Table 1. — Social-demographic characteristics of subjects in the study according to instrument used to define asthma

		Questionnaire		Bronchial challenge test	
		n	%	n	%
Asthma	No	1861	88.8	1068 [#]	92.4
	Ever	234	11.2	88	7.6
	Current	107	5.1		
	Past	127	6.1		
Area*	Barcelona	435	20.7	163	14.1
	Galdakao	523	25.0	335	29.0
	Albacete	473	22.6	254	22.0
	Oviedo	383	18.3	213	18.4
	Huelva	281	13.4	191	16.4
Age	20–24	431	20.5	260	22.5
	25–29	420	20.0	232	20.1
	30–34	414	19.8	226	19.6
	35–39	415	19.8	228	19.8
	40–44	415	19.8	210	18.2
Sex*	Female	1096	52.3	549	47.5
	Male	999	47.7	607	52.5
All		2095	100	1156	100

n: number of subjects. *: statistically significant ($p < 0.05$) differences were present in the distribution by area and sex between all subjects and those completing bronchial challenge test. #: number of subjects who reported neither ever asthma nor bronchial responsiveness, whereas ever refers to presence of both conditions.

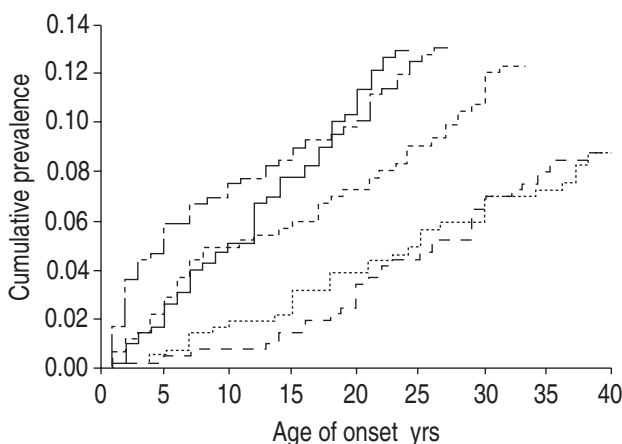


Fig. 1. — Cumulative prevalence of asthma by age of onset and cohort of birth (each year signals the middle of a 5 yr period). - - -: 1950 cohort; ·····: 1955; - · - ·: 1960; - - - -: 1965; —: 1970.

Table 2. – Prevalence of asthma by risk factors, and crude odds ratio (OR) and 95% confidence interval (95% CI)

		Age of onset							
		≤15 yrs				>15 yrs			
		Current asthma (39/1861) [#]		Past asthma (78/1861) [#]		Current asthma (68/1861) [#]		Past asthma (49/1861) [#]	
		%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
Susceptibility factors									
Sex	Female	1.3	0.46 (0.29–0.49)*	3.0	0.57 (0.36–0.92)*	5.1	2.99 (1.69–5.28)*	3.2	1.73 (0.95–3.14)
Parental asthma	Yes	6.9	5.16 (2.66–10.0)*	4.7	1.21 (0.61–2.40)	6.4	3.95 (2.32–6.70)*	7.4	4.01 (2.16–7.40)*
Atopy	Indoor	4.2	39.6 (4.84–324)*	7.1	4.84 (2.20–10.7)*	4.9	4.95 (1.59–15.3)*	3.7	2.26 (2.86–5.92)*
	Outdoor	2.4	22.2 (2.29–215)*	4.0	2.64 (0.93–7.47)	8.3	8.32 (2.88–24.2)*	6.2	3.95 (1.64–9.51)*
	Both	9.3	91.5 (11.6–723)*	16.4	12.4 (6.04–25.1)*	17.2	15.0 (6.63–45.5)*	4.3	12.4 (6.04–25.1)*
Exposures in childhood									
Older siblings	1–2	2.2	2.23 (0.76–6.51)	1.3	1.35 (0.63–2.87)	1.5	1.50 (0.73–3.05)	1.1	1.13 (0.52–2.44)
	0	1.9	1.84 (0.60–5.70)	1.8	1.83 (0.86–3.91)	1.8	1.76 (0.85–3.63)	1.0	0.94 (0.41–2.18)
LRI <5 year	Yes	11.1	9.05 (4.46–18.4)*	25.5	14.8 (9.02–24.2)*	6.2	2.16 (0.95–4.86)	0.9	0.37 (0.05–2.73)
Any animal	Yes	1.9	0.69 (0.35–1.37)	3.5	0.58 (0.36–0.94)*	3.2	1.30 (0.70–2.39)	2.6	1.06 (0.53–2.08)
Cohort of birth									
Year of birth	<1958	0.9	0.32 (0.14–0.73)*	1.7	0.29 (0.16–0.54)*	3.6	1.03 (0.63–1.68)	3.7	2.13 (1.20–3.80)*

[#]: number of cases and controls. *: p<0.05 for comparisons respect to the reference category not shown in table. LRI: lower respiratory tract infection.

Table 3. – Adjusted⁺ odds ratio for risk factors and current asthma, asthma with bronchial responsiveness (BR), and past asthma

		Current (60/1262) [#]	Asthma and BR (88/1068) [#]	Past asthma (84/1262) [#]
Parental asthma		4.53 (2.46–8.36)*	3.13 (1.78–5.54)*	2.31 (1.31–4.06)*
Atopy	Indoor	10.2 (4.21–24.6)*	5.39 (2.68–10.8)*	3.49 (1.31–4.06)*
	Outdoor	11.5 (4.64–28.5)*	5.88 (2.77–12.5)*	3.34 (1.68–6.61)*
	Both	26.9 (11.9–61.1)*	24.1 (12.9–45.4)*	7.33 (4.09–13.2)*
Older siblings	1–2	2.57 (0.93–7.09)	2.20 (0.96–5.04)	1.30 (0.63–2.68)
	0	3.26 (1.16–9.15)*	2.23 (0.95–5.27)	1.44 (0.68–3.03)

⁺: Adjusted for sex, age, area, low respiratory infections <5 yrs, and the rest of variables in the table. Age did not enter in any of the models and lower respiratory tract infections was only included in the model for past asthma, due to p<0.1.

[#]: number of cases and controls in each multivariate model. Due to missing values in atopy, numbers are lower than in table 2. *: p<0.05.

The age of onset of asthma has varied over time. The prevalence of asthma beginning up to the age of 15 yrs was higher in the more recent birth cohorts (fig. 1) although in all birth cohorts there were individuals who reported their asthma had begun after the age of 15 yrs.

Factors associated with susceptibility to current asthma beginning up to the age of 15 yrs (table 2) were the male sex, parental asthma, atopy to indoor and outdoor allergens, lower respiratory tract infections (LRTI) before the age 5 yrs, and a younger birth cohort. Asthma beginning in childhood but no longer active (past asthma) showed similar associations to risk factors as current asthma. Parental asthma as a risk factor was an exception, as the association with current and past asthma was significantly different. A statistically significant negative association was evident between having had a pet and past asthma.

Current asthma beginning after the age of 15 yrs was significantly associated with only the female sex, parental asthma and atopy (table 2). With the exception of year of birth, risk factors for current and past asthma did not differ. Adjusted associations for the rest of the variables in table 2 were similar to the crude associations shown in table 2, whatever the age of asthma onset.

The association for sex, LRTI, having had a pet and

cohort of birth was significantly different in asthma started in childhood compared to adulthood. Table 3 presents the independent association for factors that did not vary with age of onset. The strong association of atopy and parental asthma with current asthma (defined both by questionnaire and bronchial challenge) was confirmed after including all subjects whatever the age of onset. Atopy was associated to a lesser extent with past asthma than with current asthma. Having less than three older siblings was significantly associated with current asthma, suggesting that the lack of statistical significance for this factor observed when stratifying by age of onset was due to lack of statistical power.

Discussion

In this study of young adults, we assessed the risk factors related with asthma onset occurring early or later in life. Important findings arise from this analysis: firstly; atopy to perennial (indoor) and seasonal (outdoor) allergens, parental asthma, and having less than three older siblings were associated with current asthma whatever the age of asthma onset; secondly, LRTIs before the age of 5 yrs and not having had a pet in childhood were associated with asthma (both current and past)

starting in childhood but not in adulthood; and finally, the previous factors could not explain the sex differences by ageing and the lowest asthma prevalence in the oldest cohorts.

Case-control studies with prevalent cases are limited when assessing exposures that would have been modified in the past because of disease occurrence, such as indoor environment or having had a pet [17]. A second potential limitation was recall bias. In particular, subjects who have asthma may remember more accurately past episodes of childhood LRTI, such as a past pneumonia, than subjects without asthma. Information bias may also be present in reporting when asthma began, which could be postponed in time by older generations. Nonresponse may have also affected the results of our study. Individuals who did not attend the centre, did not show any difference by sex or age compared with those who participated, but more females with no symptoms declined to participate than females with symptoms. Prevalence of current asthma in females could have been artificially increased. However, our prevalence estimates were similar to those observed using all subjects who participated in the first phase of the ECRHS [18], who were 85% of the selected, and also to other studies [19]. Adjustment for nonresponse did not result in substantial changes of the prevalence of respiratory symptoms in the ECRHS [20]. Inclusion of bronchial responsiveness in the definition of cases reduces the diagnostic misclassification, but at the cost of increasing nonresponse. In general, our findings for current reported asthma and for reported asthma with bronchial challenge were in substantial concordance.

The strong association of asthma with atopy has been well described previously [21]. We found a strong association with sensitization to seasonal allergens, with a magnitude similar to that for perennial allergens both in current and past asthma. In children, seasonal allergens are believed to be unrelated to asthma [22]. In this study we found a significant association, though we measured atopy in adulthood. Outdoor allergens in adults have been related with epidemic and endemic presentations of emergency room admissions for asthma [23, 24]. This suggests that seasonal allergens might have an important role in asthma during adulthood, as we found in the analysis of the independent association of common aeroallergens with bronchial responsiveness [25]. The association between asthma and atopy was stronger for current asthma than for past asthma. We could not exclude the possibility that the lack of temporal coincidence between measurement of atopy and occurrence of asthma symptoms explained this difference. An alternative explanation for the lower association of atopy with past asthma, and to a lesser extent to parental asthma and family size, is that there was a higher rate of misclassification for past asthma.

LRTI in childhood was associated with a high risk of onset of asthma in adulthood, while birth order was inversely associated. Respiratory infections, in particular those leading to bronchiolitis, might be a risk factor for asthma [8]. We performed a retrospective study of LRTI in childhood with a unique question on "important respiratory infections". The lack of specificity of a single question and the possible recall bias weakens the validity of our finding. An inverse association with birth

order, explained by a higher frequency of secondary infections in larger families, has been reported previously with wheezing in children [26], coinciding with reports of an association between birth order [27–28] or family size [29] and hay fever. This contradictory pattern may be related to the timing (or the type) of infections in childhood.

We found an inverse association with having had a pet during childhood (whatever the pet, data not shown). Having a pet has been considered a risk factor for asthma attacks [30], but also protective in rural children [31]. Our finding could be due to a self-selection of symptomatic subjects who avoided having a pet.

Gender differences in asthma according to age of onset coincided with previous studies [19]. We cannot exclude, however, the possibility that the higher prevalence in adult women was in part due to a self-selection of nonresponders. An increase of asthma prevalence in younger generations is another relevant finding in this paper. This increase is not explained by variations in atopy, family size, parental asthma, LRTI, or having a pet. Alternative explanations such as changes in the labelling of asthma in recent years or in the vaccination policy could not be ruled out. Recently, changes in the vaccination policy have been postulated as potentially influencing the prevalence of asthma [32]. This information was not available from the ECRHS.

In addition to the known risk factors of asthma (atopy to perennial allergens, parental asthma), we have provided evidence for an association of asthma (whatever the age of onset) with sensitization to seasonal allergens, and having less than three older siblings. There was also an association of childhood asthma with lower respiratory tract infection.

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