ORIGINAL ARTICLES

Asthma Incidence in Huelva, Spain at 2 Stages of Life: Childhood and Young Adulthood

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OBJECTIVE: Few studies have evaluated the incidence of asthma in Spain. Although more children than adults develop asthma every year, no study to date has analyzed the differences in incidence by following 2 age cohorts in the same geographical area. The aim of this study was to determine changes in wheezing, bronchial hyperreactivity, and asthma (in terms of onset, persistence, and remission), changes in forced expiratory volume in 1 second (FEV_1), and asthma incidence in children (11-16 years) and young adults (20-44 years) in the city of Huelva, Spain.

PATIENTS AND METHODS: We analyzed data from 2 groups studied for the first time between 1991 and 1993 and for the second time after an average of 9 years. In the first period, data came from the Study of Respiratory Diseases in Huelva (714 children) and the European Community Respiratory Health Survey conducted in the city (271 adults). Both groups answered a respiratory symptom questionnaire, underwent spirometry testing, and completed a nonspecific bronchial challenge test with methacholine.

RESULTS: In adults, onset was more common than remission for both wheezing (15.7% vs 6.9%, *P*=.011) and bronchial hyperreactivity (10.1% vs 3%, *P*=.017), and asthma incidence was 4.76 cases/1000 person-years. In children, there were more new cases than remissions for wheezing, (24.2% vs 4.3%, *P*=.001), bronchial hyperreactivity (13.9% vs 5.4%, *P*=.02), and asthma (9.3% vs 3%, *P*=.004). The incidence rate for asthma was 15.69 cases/1000 person-years in this age group. The annual decrease in lung function (FEV_1) was highest in adults with wheezing (34.3 mL) and asthma (54.8 mL).

CONCLUSIONS: There were more new cases of wheezing and bronchial hyperreactivity than remissions in both children and young adults. Children had a 3.3-fold higher incidence of asthma than adults in Huelva.

Key words: *Asthma. Incidence. Age. Children and adults.*

Incidencia de asma en 2 etapas de la vida: niños y adultos jóvenes de la ciudad de Huelva

OBJETIVO: Hay pocos estudios que valoren la incidencia de asma en nuestro país. Se sabe que es mayor en niños que en adultos, pero esta diferente incidencia no se ha comprobado mediante el seguimiento de 2 poblaciones de diferente edad en el mismo ámbito geográfico. El propósito de este trabajo ha sido determinar los cambios (aparición, persistencia y remisión) de sibilancias, hiperreactividad bronquial (HB) y asma, la evolución del volumen espiratorio forzado en el primer segundo y la incidencia anual de asma en niños (11-16 años) y adultos jóvenes (20-44 años) en la ciudad de Huelva.

PACIENTES Y MÉTODOS: Se ha realizado una segunda evaluación en el seguimiento de 2 grupos estudiados entre 1991 y 1993 (714 niños del Estudio de Enfermedades Respiratorias de Huelva y 271 adultos del Estudio Europeo de Enfermedades Respiratorias), con un promedio de tiempo de 9 años. Se pasó a ambos grupos un cuestionario sobre síntomas respiratorios, además de efectuar una espirometría y una prueba de provocación bronquial inespecífica con metacolina.

RESULTADOS: En los adultos se encontraron más nuevas apariciones (15,7%) que remisiones (6,9%) de sibilancias (p = 0,011) e HB (apariciones: 10,1%; remisiones: 3%; p = 0,017), con una incidencia anual de asma de 4,76 casos/1.000 personas-año. Los niños mostraron más nuevas apariciones (24,2%) que remisiones (4,3%) de sibilancias (p < 0,001), HB (un 13,9% de apariciones y un 5,4% de remisiones; p = 0,02) y asma (un 9,3% de apariciones y un 3% de remisiones; p = 0,004), con una incidencia anual de asma de 15,69 casos/1.000 personas-año. La pérdida anual de función pulmonar (volumen espiratorio forzado en el primer segundo) fue más elevada en los adultos en los que aparecieron sibilancias (34,3 ml) y asma (54,8 ml).

CONCLUSIONES: En ambas poblaciones, hay más nuevos casos de sibilancias e HB que remisiones. La incidencia anual de asma es 3,3 veces mayor en niños que en adultos en la ciudad de Huelva.

Palabras clave: *Asma. Incidencia. Edad. Jóvenes y adultos.*

Introduction

The incidence of a disease is the number of new cases appearing in a population over a given period of time. Incidence is a dynamic index whose measure requires following a target population over time. When used to

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describe recurring disease, incidence is generally calculated on the basis of first episodes. It can be studied by performing a longitudinal study of a population or by studying 2 cohorts at 2 different moments in time.

The European Community Respiratory Health Survey was conducted for the first time between 1991 and 1993 (ECRHS-I)[1] and repeated in 1999 and subsequent years (ECRHS-2).[2] One of the aims of the second phase of the study was to determine asthma incidences in different countries. This was done by repeating a respiratory symptom questionnaire and lung function tests in a population after an average of 9 years.[2] One of the findings of the ECRHS, reported by Sunyer et al,[3] was that the incidence of asthma had increased by a similar magnitude in the majority of industrialized countries studied. In Spain, the incidence was seen to increase slightly, with new cases outnumbering remissions, following an analysis of the onset, persistence, and remission of several variables (wheezing, bronchial hyperreactivity, and a combination of both).[4] Our group, based in Huelva, Spain, participated in the ECRHS together with groups from 4 other Spanish cities (Albacete, Barcelona, Oviedo, and Galdakao).[5] The age of our adult cohort in the initial phase of the study (1991-1993) was 20 to 44 years. We also studied a cohort of children aged 11 to 16 years using the same methods.[6-8]

To the best of our knowledge, there are no data on the incidence of asthma in children in Spain. As part of the first phase of the International Study of Asthma and Allergies in Childhood (ISAAC), García-Marcos et al[9] studied the prevalence of asthma in children (aged 6-7 years and 13-14 years), although the method they used was somewhat different from ours as the initial age brackets were maintained throughout subsequent phases of the study by incorporating new groups of children and adolescents. While the findings of ISAAC provide interesting insights into changes in asthma prevalence in certain age groups, they do not provide information on incidence, given that new populations in the same age brackets were recruited during each phase. That cross-sectional study of 2 cohorts of children of different ages showed that, over a period of 8 years, the prevalence of asthma increased substantially in the 6-to-7-year-old group but only marginally in the 13-to-14-year-old group.

We compared the incidence of asthma in Huelva at 2 stages of life by studying children and young adults between 1991 and 1993 and again in 2002. The aim of this study was to determine changes in wheezing, bronchial hyperreactivity, and asthma (in terms of onset, persistence, and remission) in children and young adults and changes in forced expiratory volume in 1 second (FEV_1) in young adults. We also established the annual asthma incidence among both children and young adults in Huelva.

Patients and Methods

We performed a follow-up study of 2 cohorts who had been studied for the first time between 1991 and 1993. The subjects were children (n=714) from the Study of Respiratory Diseases of Huelva[6-8] and young adults (n=271) from the ECRHS-I conducted in Huelva.[5] Their ages at the time of the first study were 11 to 16 years and 20 to 44 years, respectively. Both studies were performed in the same population samples, which had been drawn from the general population in Huelva using similar random sampling methods. Adults had been stratified by age and sex from the electoral roll of the city of Huelva, and children had been recruited via cluster sampling among local pupils.

We performed a study of nonresponders to compare those who participated in both phases to those who only participated in the first one in order to determine whether the follow-up participation rate might have caused selection bias.

In this second phase, the participants were administered the same respiratory symptoms questionnaire as in the first study[5,10] and were also required to undergo spirometry, a nonspecific bronchial challenge test with methacholine, and a range of other tests. We also analyzed whether patients had current wheezing, defined as the presence of wheezing in the last 12 months. Bronchial hyperreactivity was defined as a decrease of more than 20% in FEV_1, in comparison with the response after the administration of saline, following methacholine challenge to a cumulative dose of 5.117 µmoL or an extrapolated dose of 8 µmoL. From an epidemiologic perspective, patients were considered to have asthma if they had current wheezing and a positive methacholine challenge result.[11,12]

Wheezing, bronchial hyperreactivity, and asthma were considered to be of new onset if they were observed for the first time in the follow-up study (9-10 years after the first study in 1991-1993). Asthma was considered to be persistent when results were positive in both studies, and in remission when present in the first study but not in the second one.

Statistical Analysis

Changes (onset or remission) were studied using the pairwise McNemar test to compare the results of the 2 studies. The annual incidence of asthma was estimated by dividing the total number of cases of new-onset asthma (present in the second study but not in the first one) by the total person-years accumulated during the intervening period between the studies by those who did not initially have asthma. The time between the first and the follow-up study was calculated for each individual.

The incidence density ratio was calculated as the ratio between incidence in children and young adults. Log-transformation was used to calculate the 95% confidence interval (CI) for the incidence density ratio.[13]

Results

We examined 393 children (55% response rate) and 204 adults (75.3% response rate) in the second study, performed after an average of 9 years. The table shows the results of the study of nonresponding children and adults in comparison with participants to determine whether response rates in the second study might have caused selection bias. Thus, we compared those who participated in the second phase of the study (393 children and 204 adults) with those who did not (321 children and 67 adults) in terms of sex and frequency of symptoms. As can be seen, there were no differences between the participating and nonresponding individuals in the adult cohort in terms of sex or frequency of symptoms, bronchial hyperreactivity or asthma, indicating that selection bias was not present. In the cohort of children, the percentage of boys was

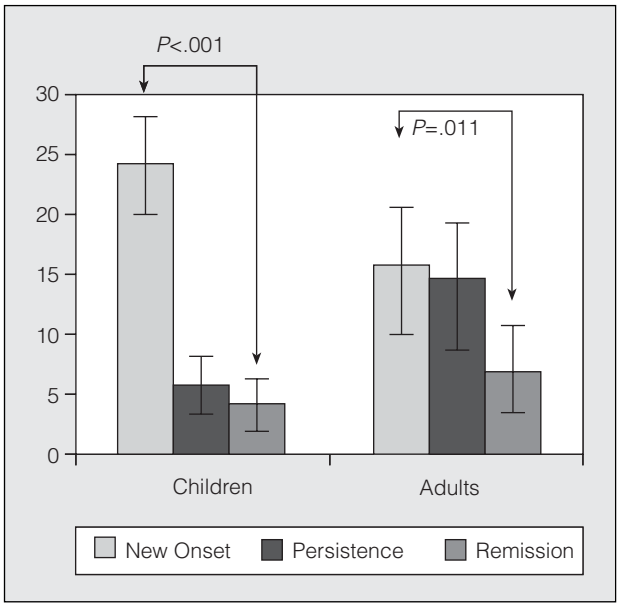

Figure 1. Wheezing onset, persistence, and remission (%) in children and adults.

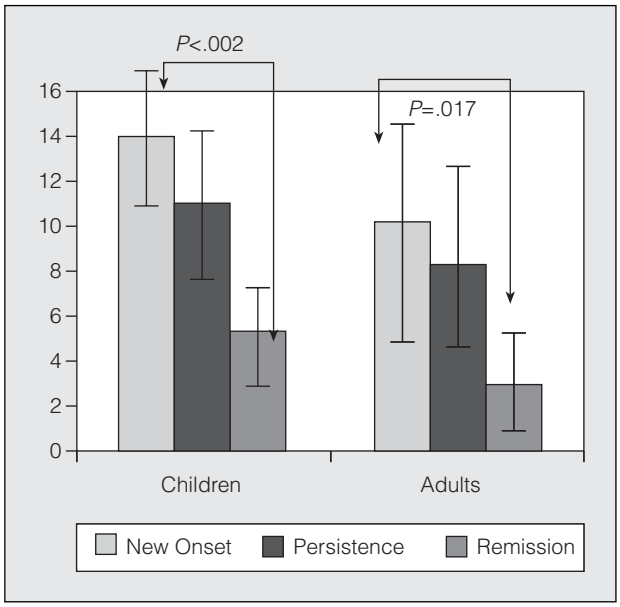

Figure 2. Bronchial hyperreactivity onset, persistence, and remission (%) in children and adults.

smaller in the group of participants in both studies (59%) than in those who participated only in the first study (47.8%), and the prevalence of bronchial hyperreactivity and wheezing combined was higher in children who participated in both studies (5.36%) than in the nonresponders (1.26%), although the difference was not significant for either bronchial hyperreactivity or wheezing in isolation. Asthma was somewhat more common in boys (4.9%) than in girls (3%) in the first study but less common in boys in the second study (9.5% vs 13.7% for boys and girls, respectively).

Figures 1 to 3 show the percentage of children and adults with wheezing, bronchial hyperreactivity, and asthma (wheezing and bronchial hyperreactivity) in terms of onset, persistence, and remission. In children, onset was more common than remission for wheezing (Figure 1), bronchial hyperreactivity (Figure 2), and asthma (Figure 3), which was defined as the presence of wheezing in the preceding year combined with a positive methacholine challenge test.[11,12] Of the children who did not report wheezing in the 12 months prior to the first study, 24.2% reported this symptom in the second study. Only 4.3% of those who reported wheezing in the first study did not do so in the second one. Accordingly, wheezing onset was more common than remission (P<.001), as were onset of bronchial hyperreactivity (P<.02) and asthma (P=.004).

In adults, although onset was also more common than remission for wheezing (P=.011) and bronchial

Study of Subjects Who Participated in the First Phase But Who Did Not Respond to the Call to Participate in the Second Phase

	Children (n=714)					Adults (n=271)				
	Did Not Respond[a] (n=321)		Responded[b] (n=393)			Did Not Respond[a] (n=67)		Responded[b] (n=204)		
	No.	%	No.	%	*P*	No.	%	No.	%	*P*
Men	138	59	187	47.8	0.007	36	53.7	99	49.8	.46
Tightness in chest on awakening	21	6.9	38	10.1	0.134	11	16.4	29	14.2	.66
Chronic cough	75	23.6	85	22	0.62	14	20.9	49	24	.60
Night coughing	65	21	82	21.5	0.89	20	29.9	62	30.4	.93
Eczema or skin allergies	72	23.5	89	23.8	0.94	21	31.3	83	40.7	.17
Wheezing	28	8.7	40	10.2	0.5	15	22.4	44	21.6	.89
Bronchial hyperreactivity	27	12.1	60	16	0.19	6	11.5	21	11.8	.95
Wheezing and bronchial hyperreactivity	4	1.26	21	5.36	0.004	2	3.2	11	5.5	.46

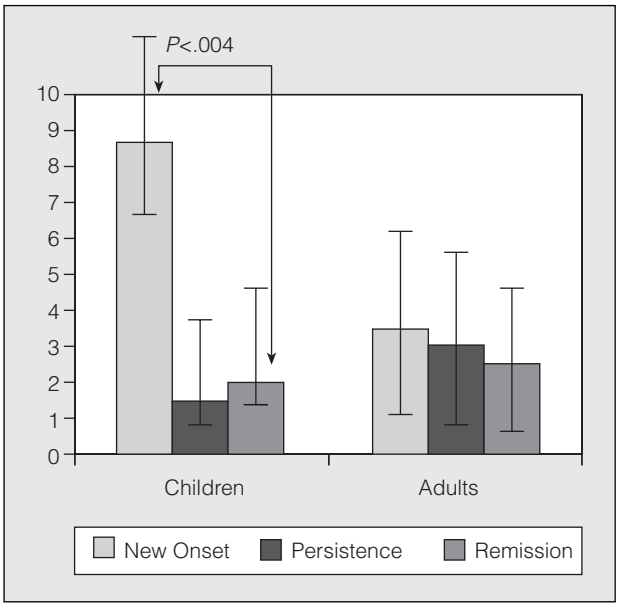

Figure 3. Asthma (wheezing in the last 12 months and bronchial hyperreactivity) onset, persistence, and remission (%) in children and adults.

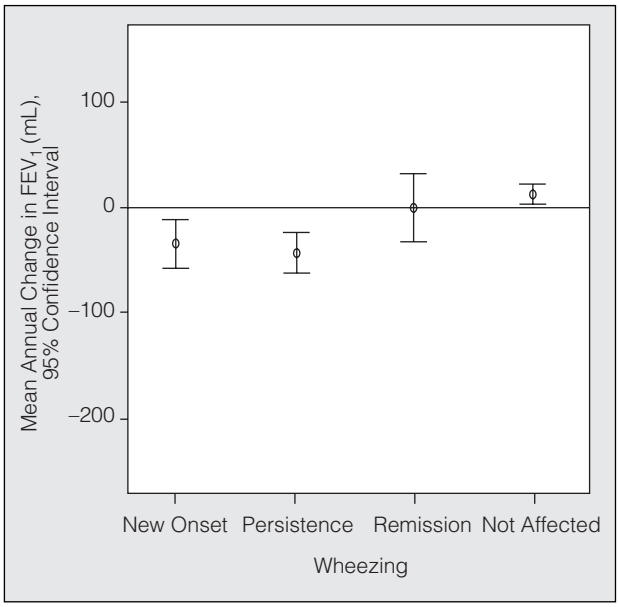

Figure 4. Adults: Mean annual change in forced expiratory volume in 1 second (FEV_1) with respect to changes in wheezing.

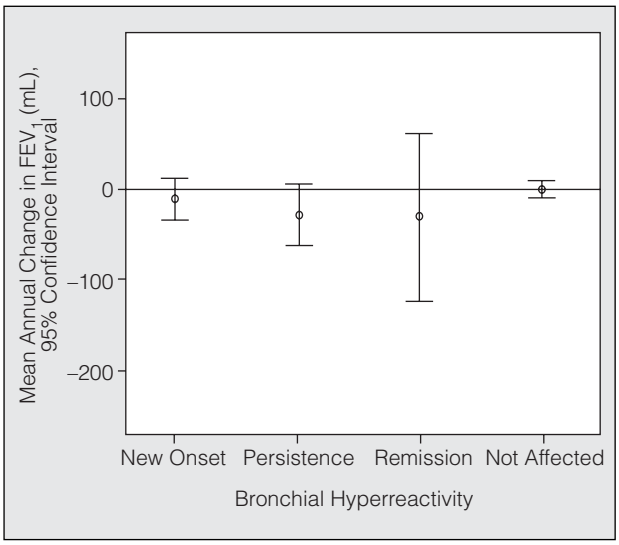

Figure 5. Adults: Mean annual change in forced expiratory volume in 1 second (FEV_1) with respect to changes in bronchial hyperreactivity.

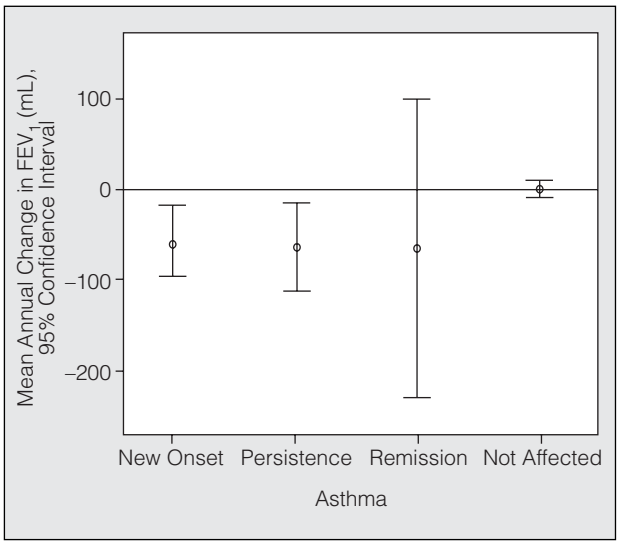

Figure 6. Adults: Mean annual change in forced expiratory volume in 1 second (FEV_1) with respect to changes in asthma diagnosis.

hyperreactivity (*P*=.017), there were no significant differences in asthma diagnosis from one study to the next.

For children, the cumulative annual incidence was 41.73 cases per 1000 person-years (95% CI, 33.4-50.1 cases) for wheezing, 25.83 cases (95% CI, 18.9-32.8 cases) for bronchial hyperreactivity, and 15.69 cases (95% CI, 10.7-20.7 cases) for asthma diagnosis. The corresponding rates for adults were 25.01 cases per 1000 person-years (95% CI, 16.30-33.70 cases) for wheezing, 13.40 cases (95% CI, 7.10-19.70 cases) for bronchial hyperreactivity, and 4.76 cases (95% CI, 1.20-8.30 cases) for asthma diagnosis.

Cumulative wheezing incidence was 1.67 times higher (95% CI, 1.11-2.51) in children than in adults. For bronchial hyperreactivity, it was 1.93 times higher (95% CI, 1.12-3.34), and for asthma, 3.3 times higher (95% CI, 1.47-7.4).

In adults, the annual change in FEV_1 (mL) in relation to wheezing (Figure 4) varied. While FEV_1 deteriorated progressively in patients with new-onset wheezing (–34.3 mL) and persistent wheezing (–43.1 mL), it improved

slightly in those without wheezing (12.1 mL). No changes were observed in patients in remission. Changes therefore differed in these groups (analysis of variance [ANOVA], $P<.001$). We were unable to find a clear pattern in terms of FEV_1 changes in patients with bronchial hyperreactivity or evidence of between-group differences (Figure 5). Finally, the trend was for an annual decline in FEV_1 in patients with new-onset asthma (–54.8 mL) and persistent asthma (–61.3 mL) (Figure 6). In contrast, no changes were observed in patients in remission or without asthma (ANOVA, $P=.001$).

Discussion

We analyzed changes in respiratory symptoms (wheezing) and objective measures of bronchial hyperreactivity in 2 age cohorts (children and young adults) after an interval of 9 years. Both phases of the study were conducted using the same methods. We found more cases of onset than remission for wheezing, bronchial hyperreactivity, and asthma in children. The trend was similar for wheezing and bronchial hyperreactivity in adults but not for asthma (no significant changes observed).

Monitoring the course of a chronic, intermittent disease such as asthma poses several problems. Asthma symptoms, for example, can appear and disappear over the years. This is part of the natural history of the disease but it can lead to contradictory findings in populations studied at different moments in time. As Basagaña et al[4] reported, patients can state in an initial study that they have never had asthma, yet in a follow-up study, report that they have had asthma or experienced wheezing for over 10 years. In an attempt to overcome this problem, we analyzed changes in current wheezing (in the preceding 12 months) in order to minimize recall bias and include an objective measure of bronchial hyperreactivity. Finally, we examined changes in epidemiologically diagnosed asthma, defined as the presence of both wheezing and bronchial hyperreactivity.[11,12]

We studied 2 cohorts (children and young adults) in an initial study and again 9 years later. Although this design is difficult in that the completion of a questionnaire and the performance of objective tests are required, the response rate in our case was comparable to that of most studies in similar age groups and follow-up periods.[4,14,15]

Wheezing and bronchial hyperreactivity were observed in more children who participated in both studies than in those who participated only in the first study, although the difference was not significant. Likewise, we detected no difference in the adult group, meaning that selection bias can be excluded. The risk of selection bias, in any case, was minimized by the design of our study, which compared 2 cohorts at different times. Selection bias would have been a problem had we sought to analyze prevalence rather than incidence. In view of the participation rate, particularly in the group of children, we considered that it was important to carry out a study of nonresponders to check that those who completed the follow-up phase of the study did not exhibit substantial differences, in terms of frequencies of symptoms, from those who only participated in the first phase. Although this was reasonably demonstrated for symptoms, we did see that there were fewer boys and fewer patients with asthma (wheezing and hyperreactivity) in the second study than in the first. Asthma was somewhat more common in boys than in girls in the first study and less common in the second study, although the differences were not significant. Asthma incidence in children might, therefore, be slightly overestimated because more girls than boys participated in the second phase of the study. Although more new cases of asthma were found in the first study, it should be borne in mind that incidence is of course being measured among those who did not have asthma initially. Another problem, which is more difficult to control for in studies of this type, is that patients who develop symptoms during the period between the 2 studies might tend to participate more in the second study. In summary, while our figures for the incidence of asthma in the children who participated in our study are reliable, extrapolation might overestimate the incidence in the general population.

Our results do reflect, however, a real increase in respiratory symptoms and bronchial hyperreactivity, in particular, in children. Wheezing and bronchial hyperreactivity changed significantly between the first and second studies in adults, albeit to a lesser degree than in children. Asthma diagnosis, in contrast, did not change.

In an article published in 2001, Basagaña et al[4] reported results for the incidence of asthma in young adults (20-44 years old), studied in 5 Spanish cities for the first time in 1991 and followed for an average of 6.75 years. This arm of the ECRHS study found the overall incidence to be 5.53 cases per 1000 person-years, with incidence rates ranging from 3.50 cases in Galdakao to 7.87 in Huelva ($P=.40$). It is interesting to note that the incidence was highest in individuals who did not have self-reported asthma in the first phase of the study but did have hyperreactivity, positive immunoglobulin E to pollen, and various symptoms (such as wheezing) that would be indicative of asthma. Of these symptoms, bronchial hyperreactivity was the strongest predictor of asthma onset. When these individuals were excluded from the analysis, the incidence decreased from 5.53 to 1.50 cases per 1000 person-years. For the same age group (young adults aged 20-44 years in 1991 and followed for 9-10 years), our study found a similar asthma incidence of 4.76 cases per 1000 person-years in Huelva. Like Basagaña et al, we only required that the patients did not "have asthma" in the first study.

Torén et al[16] reported a low to medium asthma incidence in northern Europe (Sweden, Norway, Denmark, Iceland, and Estonia) on studying young adults between 1989 and 2001. Their study population was of a similar age to ours (20-44 years at the beginning of the study and 30-54 years at the end). The authors reported an incidence of 2.2 cases of asthma per 1000 person-years, which is lower than our rate of 4.76 cases. They excluded patients who stated in the first study that they had experienced asthma attacks, taken asthma medication, or ever had asthma. Like

Basagaña et al,[4] they excluded from the follow-up study patients who reported respiratory symptoms in the first study, even if they stated that they had never had asthma. Asthma incidence reported by studies in other countries, such as the United States,[17] Scandinavia,[18] and Italy,[19] ranges from 1 to 5 cases per 1000 person-years.

We found a high prevalence of symptoms indicative of asthma (wheezing in particular) in Huelva in 1991.[5] As has been indicated by other authors, in longitudinal studies, asthma incidence is highest in people who report previous respiratory symptoms,[4,16] and this might explain why our incidence rates are among the higher values reported in the literature.

It is noteworthy that incidence rates reported by studies performed in the 1980s are higher than those reported by more recent studies. In 1989, for example, Stewart et al[20] published the results of a Canadian study that found an incidence of 6 cases per 1000 person-years for men and 12 cases per 1000 person-years for women in a population aged 25 to 54 years. Torén et al,[16] in a discussion of their work, suggested that the incidence of asthma has been declining in recent years.

Like Basagaña et al,[4] we would like to draw attention to the fact that the incidence in countries with a low to medium prevalence of asthma, such as Spain, is similar to the rates in countries with a higher prevalence, such as England and the USA.[21] This could be because factors related to adult-onset asthma might be different from those related to disease duration. In other words, factors related to adult-onset asthma might be common to all regions while those related to disease duration or early-onset asthma might vary from one region to the next.

Asthma incidence varies with age and is known to be higher in children than in adults. In Huelva, we found that asthma incidence was 3.3 times higher in children than in young adults. On studying a group of patients aged 12 to 41 years in a longitudinal study performed in Denmark over 8 years, Thomsen et al[22] found an incidence of 4.5 cases per 1000 person-years for men and 6.4 cases per 1000 person-years for women. They also showed that the incidence rate clearly decreased with age and reached a plateau at 20 years; their findings were very similar to ours.

The higher incidence of asthma in young people may have several explanations in addition to the natural history of the disease. As suggested by Genuneit et al,[23] one possibility is the effect of smoking. In our study, the possible impact of smoking both on respiratory symptoms (and wheezing in particular) and on bronchial hyperreactivity was more evident in age groups in which children tend to start smoking (average age of onset of 13-15 years). In the group of young adults, the number of smokers was similar in both phases of the study (1991 and 2001). Finally, wheezing was more closely related to a diagnosis of asthma in children than in adults, for whom differential diagnoses such as chronic obstructive pulmonary disease were considered.

In summary, the incidence of asthma in Huelva was higher in children than in young adults, coinciding with findings of studies performed in other populations.

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