Geographic Variation in the Prevalence of Asthma Symptoms in Spanish Children and Adolescents. International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3, Spain

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OBJECTIVE: To analyze geographic variations in the prevalence of symptoms related to asthma in Spanish children and adolescents.

POPULATION AND METHODS: In 2001 and 2002, the Spanish arm of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3 collected information on 28 445 children in the age bracket of 6-7 years in 10 metropolitan areas (A Coruña, Asturias, Barcelona, Bilbao, Cartagena, Castellón, Madrid, Pamplona, San Sebastián, and Valencia) and on 31 257 adolescents in the bracket 13-14 years in 11 areas (the previously named areas plus Valladolid). An asthma symptom questionnaire was filled in by parents or the adolescents themselves. Differences in symptoms between geographic areas were analyzed by fitting a logistic regression model. The relationship between symptoms and age was analyzed by linear correlation.

RESULTS: The prevalence of recent wheezing (last 12 months) ranged from 7.1% to 12.9% among 6-7-year-olds and from 7.1% to 15.3% among the 13-14-year-olds. The greatest risk of recent wheezing was observed for children in A Coruña (odds ratio [OR] =1.96 in comparison with the area of lowest prevalence; 95% confidence interval [CI], 1.65-2.33) and Bilbao (OR=1.83; 95% CI, 1.54-2.18) and for adolescents in A Coruña (OR=2.38; 95% CI, 2.04-2.79) and Asturias (OR=2.37; 95% CI, 2.03-2.77). A strong correlation (r=0.72) was observed between the prevalence of recent wheezing and age in each of the geographic areas.

CONCLUSIONS: Considerable geographic variation in the prevalence of asthma symptoms can be seen in Spain even among young children. Symptoms are more frequent in children and adolescents who live on the Spain's northern Atlantic coast.

Key words: *Asthma. Prevalence. ISAAC. Child. Adolescent.*

Variaciones geográficas en la prevalencia de síntomas de asma en los niños y adolescentes españoles. International Study of Asthma and Allergies in Childhood (ISAAC) fase III España

OBJETIVO: Analizar las variaciones geográficas en la prevalencia de síntomas relacionados con el asma en niños y adolescentes españoles.

POBLACIÓN Y MÉTODOS: Durante los años 2001 y 2002, el International Study of Asthma and Allergies in Childhood (ISAAC) fase III estudió a 28.445 niños de 6-7 años de 10 áreas (A Coruña, Asturias, Barcelona, Bilbao, Cartagena, Castellón, Madrid, Pamplona, San Sebastián y Valencia) y 31.257 adolescentes de 13-14 años de 11 áreas (las anteriores más Valladolid) españolas. Los síntomas de asma se recogieron en un cuestionario escrito completado por los padres de los niños o por los propios adolescentes. Las variaciones geográficas de las prevalencias de los síntomas se analizaron con un modelo de regresión logística y su correspondencia por edad mediante correlación lineal.

RESULTADOS: La prevalencia de sibilancias recientes (últimos 12 meses) varió entre el 7,1 y el 12,9% a los 6-7 años, y entre el 7,1 y el 15,3% a los 13-14 años. El riesgo más elevado (*odds ratio* [OR] respecto al área de menor prevalencia) de presentar sibilancias recientes correspondió a los niños de A Coruña (OR = 1,96; intervalo de confianza [IC] del 95%, 1,65-2,33) y Bilbao (OR = 1,83; IC del 95%, 1,54-2,18) y los adolescentes de A Coruña (OR = 2,38; IC del 95%, 2,04-2,79) y Asturias (OR = 2,37; IC del 95%, 2,03-2,77). Se comprobó una fuerte correlación por edad en las prevalencias de sibilancias recientes de cada área geográfica (r = 0,72).

CONCLUSIONES: En España existen, desde edades tempranas, variaciones geográficas notables en la prevalencia de síntomas de asma. Éstos son más frecuentes en los niños y adolescentes que habitan en la fachada atlántica del país.

Palabras clave: *Asma. Prevalencia. ISAAC. Niño. Adolescente.*

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Introduction

International research leaves little room for doubt that there are geographic variations of considerable magnitude in the prevalence of asthma during childhood and adolescence.[1] The best evidence on this aspect of the epidemiology of asthma, an issue pertinent to both public health and respiratory medicine, has come from the International Study of Asthma and Allergies in Childhood (ISAAC).[2,3] In phase 1 of the study, which ended in 1996, the ISAAC investigators reported the prevalences of recent wheezing (last 12 months) for 56 countries, revealing rates up to 5-fold higher in some child populations in the 6-7-year-old age bracket and up to 15-fold higher in adolescents in the 13-14-year-old bracket.[4] The extraordinarily great differences and the complexities of the pattern of international distribution revealed by the ISAAC study provides a clear indication that environmental factors in the broadest sense of the phrase play a role in the development of the disease.[5] Analyzing territorial variations in the prevalence of asthma symptoms has not only descriptive value, from this standpoint, but it also allows us to hypothesize on the factors responsible for the distribution of the disease.[2,5]

In Spain the phase 1 ISAAC survey found that the prevalences of recent wheezing calculated based on a written questionnaire ranged from 3.5% to 8.4% in children in the age bracket of 6-7 years and from 5.5% to 14.6% in adolescents in the 13-14-year-old bracket in a series of population centers around the country.[4] Thus, although the prevalence rates for Spain overall were in the low-to-middle range in comparison with other countries, the rates for asthma symptoms for some areas such as Barcelona, Cartagena, Cádiz, or Bilbao easily doubled those of other Spanish cities such as Pamplona, Valladolid, or Castellón. A detailed analysis of the ISAAC phase 1 findings for adolescents of 9 of the geographic areas suggested that there are 2 patterns of asthma distribution in Spain: the first pattern is found around the perimeter (coastal areas), where there is a relatively high prevalence, and the second is characteristic of the interior (both high plains areas), where the prevalence is comparatively low.[6] Unfortunately that analysis did not include children in the age bracket of 6-7 years because they were simultaneously surveyed in only a few geographic areas, a circumstance that has until now prevented assessment of whether the 2 patterns of prevalence for Spain are also reflected at that early age.

During the 2-year period of 2001-2002, the phase 3 ISAAC investigation was carried out in Spain with the main objective of analyzing changes over time in the prevalence of asthma symptoms and allergic diseases since phase 1 of 1994-1995.[7] The Spanish phase 3 ISAAC survey included groups of children and adolescents in population centers that had not been studied before, giving us the opportunity to push forward in the description of geographic differences in asthma in this country. To that end, the contributors to this study aimed to describe and analyze the prevalence of asthma symptoms in Spanish children and adolescents and the variations from one participating population center to another.

Populations and Methods

Phase 3 of the Spanish ISAAC study brought together the work of 11 research groups in as many geographic areas of the Iberian Peninsula. Each group implemented the phase 3 protocol (http://isaac.auckland.ac.nz) in their own area. The target population consisted of children in the age bracket of 6-7 years in 10 areas in Spain (A Coruña, Asturias, Barcelona, Bilbao, Cartagena, Castellón, Madrid, Pamplona, San Sebastián, and Valencia) and adolescents in the bracket of 13-14 years living in 11 areas (all the aforementioned population centers plus Valladolid). The scope of the representative population sample for each ISAAC center was as follows: provincial in Asturias and Valladolid; local, complemented if necessary by taking subjects from outlying towns in A Coruña, Bilbao, Cartagena, Castellón, Pamplona, San Sebastián, and Valencia; and city district wide in Barcelona and Madrid (the health care areas of Hospital del Mar in Barcelona and Hospital 12 de Octubre in Madrid). With the exception of San Sebastián, a population sample of 3000 subjects per age bracket was defined prospectively to provide a statistical power that would allow differences in prevalence on the order of 2% to be detected with a significance level of 1%.

For practical reasons, the field work was carried out in schools, and recruitment was restricted to students in the first or second grade of primary school (ISAAC age bracket of 6-7 years) and of students in their second or third year of secondary school education (ISAAC age bracket of 13-14 years). In each geographic area, each ISAAC center obtained the approval of the appropriate local education authorities and invited selected schools to participate. Once the cooperation of the schools had been promised, the project was explained to the parents of all children and adolescents in the selected grades in a letter in which the terms "asthma" and "allergy" were avoided. The letter was accompanied by a form for giving consent to enrollment in the study. The Spanish version of the ISAAC phase 3 study protocol and the operational plan for implementing it was approved by the regional clinical research ethics committee of Asturias.

In the present study subjects in both age brackets—6-7 years old and 13-14 years old—answered the written asthma symptoms questionnaire developed and previously validated by the ISAAC steering committee.[3,8] The language used was usually Spanish (98.1% of the valid questionnaires) although Euskera was used by some of the subjects in Pamplona and Valencian by some in Castellón (1.1% and 0.8% of the valid questionnaires, respectively). Parents completed the questionnaires at home for children in the 6-7-year bracket, whereas adolescents completed their own at school. The content of the questionnaires, the same for both groups, was based on the bronchial symptoms specified by the International Union Against Tuberculosis and Lung Diseases.[9] Eight questions on the prevalence and severity of various asthma-related symptoms were included (Appendix). For the present study, which focused on asthma symptoms, questions were asked about wheezing, exercise-related wheezing, nocturnal wheezing and coughing during the "last 12 months" or at any time in the subject's history—

specifically, if the symptoms had "ever" been present or asthma had "ever" been suffered. Recent wheezing and a history of wheezing were interpreted as evidence of current and cumulative prevalences of asthma,[4,10-12] respectively, and reporting ever having had asthma was interpreted as reflecting a medical diagnosis.[10]

Following the international timetable for the ISAAC study, field work was carried out in each geographic area during the school terms corresponding to 2001 and/or 2002. ISAAC phase 3 in Spain achieved an overall participation rate of 72.3% for children in the 6-7-year bracket and 88.5% for adolescents in the 13-14-year bracket; participation ranged from 53.4% to 89.0% for children and from 75.8% to 100.0% for adolescents. The responses were processed at a central location, the ISAAC center at Cartagena, where optical mark recognition software was used (Remark Office OMR 5.0, Principia, Paoli, Pennsylvania, USA). Data was then entered into a database (Epi-Info 3.2, Centers for Disease Control, Atlanta, Georgia, USA) for forwarding to the international ISAAC data center. A total of 59 702 subjects (28 445 children aged 6-7 years and 31257 adolescents aged 13-14 years) were recruited. From that sample 238 (0.4%) were excluded from analysis because important personal information such as age and/or sex were missing from the questionnaire or because they did not respond to an item on the written asthma questionnaire, in which case it was considered blank.

Statistical Analysis

Following the ISAAC recommendations for the calculation of prevalences with a 95% confidence interval (CI), all possible responses were counted in the denominator, even those that were lost or inconsistent.[2,4] Geographic variation was studied by logistic regression modelling within each age bracket. Questions related to recent wheezing and ever having had a diagnosis of asthma were used as the dependent variables and geographic area and sex were the independent variables, for which the lowest prevalence and female sex were used as referents in the model. For the same questions we studied the relation between age brackets and prevalences within each geographic area using simple linear correlation and least squares adjustment of the regression line. All statistical calculations were performed with the STATA 7 program (StataCorp, College Station, Texas, USA).

Results

The overall prevalences of recent wheezing in all the geographic areas studied were 9.9% for 6-7-year-old children and 10.6% for 13-14-year-old adolescents (10.8% excluding the data for Valladolid, where only the older age bracket was studied). The highest prevalence was 1.8 times higher than the lowest for children and 2.1 times higher for adolescents. The lowest prevalences were in Pamplona and Castellón and the highest in A Coruña and Asturias (Table 1). The prevalences of recent wheezing after exercise were higher for adolescents than for children. Paradoxically, in adolescents, exercise-related wheezing prevalences exceeded the rates of recent wheezing, although theoretically the latter should absorb the former. Although wheezing had interfered little with sleep in the past year, nocturnal coughing prevalences were very high in both age brackets (Table 2). Also high were reports of ever having suffered wheezing, particularly for children aged 6-7 years, for whom the overall percentage was 30.2%, higher than the 19.6% calculated for adolescents aged 13-14 years (Table 3). Finally, awareness of having ever had asthma, reported either by parents or the subjects themselves, was 11.8% in the children and 14.3% for the adolescents, with the results by region ranging from 2.0 to 2.4 times the lowest rates, which were observed in Castellón; the highest rates were in Asturias and San Sebastián.

The logistic regression model showed evident geographic differences for both children aged 6-7 years and adolescents aged 13-14 years, as shown by the odds ratios (ORs) for recent wheezing and ever having had asthma (Tables 4 and 5). The population areas that provided a reference, because they had the lowest prevalences, were Pamplona for recent wheezing in children, Castellón for recent wheezing in adolescents, and both for ever having had asthma for both age brackets. At the other extreme, the highest adjusted ORs for recent wheezing were in A Coruña, Bilbao, and

TABLE 1
Prevalence of Recent Wheezing and Exercise-Related Wheezing (Written Questionnaire)*

	Wheezing, Last 12 Months				Wheezing With Exercise, Last 12 Months			
	6-7 Years		13-14 Years		6-7 Years		13-14 Years	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
A Coruña	389	12.9 (11.7-14.2)	453	15.2 (13.9-16.6)	182	6.0 (5.2-7.0)	625	21.0 (19.6-22.5)
Asturias	347	11.5 (10.4-12.7)	455	15.3 (14.0-16.7)	169	5.6 (4.8-6.5)	607	20.4 (19.0-21.9)
Barcelona	244	8.5 (7.5-9.5)	237	8.5 (7.5-9.6)	200	6.9 (6.0-7.9)	354	12.8 (11.5-14.1)
Bilbao	369	12.2 (11.0-13.4)	368	12.8 (11.6-14.1)	196	6.5 (5.6-7.4)	628	21.8 (20.3-23.4)
Cartagena	300	11.1 (9.9-12.3)	283	9.9 (8.9-11.1)	134	5.0 (4.2-5.8)	420	14.7 (13.5-16.1)
Castellón	325	8.3 (7.5-9.2)	286	7.1 (6.3-7.9)	137	3.5 (3.0-4.1)	466	11.6 (10.6-12.6)
Madrid	220	9.4 (8.3-10.7)	266	10.1 (9.0-11.3)	126	5.4 (4.5-6.4)	446	16.9 (15.5-18.4)
Pamplona	223	7.1 (6.2-8.0)	234	8.0 (7.1-9.1)	131	4.1 (3.5-4.9)	329	11.3 (10.2-12.5)
San Sebastián	77	8.6 (6.9-10.6)	151	13.9 (11.9-16.1)	43	4.8 (3.5-6.4)	233	21.5 (19.1-24.1)
Valencia	312	9.3 (8.3-10.3)	321	10.3 (9.3-11.4)	123	3.7 (3.0-4.3)	515	16.5 (15.2-17.9)
Valladolid	—	—	240	8.2 (7.2-9.2)	—	—	436	14.8 (13.6-16.2)
Total	2.806	9.9 (9.6-10.3)	3.294	10.6 (10.2-10.9)	1.441	5.1 (4.8-5.4)	5.059	16.2 (15.8-16.7)

*CI indicates confidence interval.

TABLE 2
Prevalence of Recent Nocturnal Wheezing and Coughing (Written Questionnaire)*

	Nocturnal Wheezing in the Last 12 Months				Nocturnal Coughing in Last 12 Months			
	6-7 Years		13-14 Years		6-7 Years		13-14 Years	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
A Coruña	207	6.9 (6.0-7.8)	145	4.9 (4.1-5.6)	711	23.6 (22.1-25.2)	841	28.3 (26.6-29.9)
Asturias	177	5.9 (5.0-6.7)	152	5.1 (4.3-5.9)	637	21.1 (19.6-22.6)	859	28.9 (27.3-30.6)
Barcelona	122	4.2 (3.5-5.0)	101	3.6 (2.9-4.3)	425	14.7 (13.5-16.1)	538	19.4 (17.9-20.9)
Bilbao	189	6.2 (5.4-7.1)	165	5.7 (4.9-6.6)	628	20.7 (19.3-22.2)	576	20.0 (18.6-21.5)
Cartagena	171	6.3 (5.4-7.2)	110	3.9 (3.1-4.6)	557	20.6 (19.1-22.2)	765	26.9 (25.2-28.5)
Castellón	181	4.6 (4.0-5.3)	117	2.9 (2.4-3.4)	573	14.7 (13.6-15.8)	861	21.4 (20.1-22.7)
Madrid	123	5.3 (4.4-6.2)	128	4.9 (4.0-5.7)	506	21.7 (20.0-23.4)	456	17.3 (15.9-18.8)
Pamplona	103	3.3 (2.6-3.9)	79	2.7 (2.1-3.3)	566	17.9 (16.6-19.3)	667	22.9 (21.4-24.5)
San Sebastián	34	3.8 (2.5-5.1)	72	6.6 (5.2-8.1)	161	18.0 (15.5-20.7)	207	19.1 (16.8-21.6)
Valencia	182	5.4 (4.6-6.2)	134	4.3 (3.6-5.0)	577	17.1 (15.9-18.4)	603	19.3 (18.0-20.8)
Valladolid	—	—	91	3.1 (2.5-3.7)	—	—	821	27.9 (26.3-29.6)
Total	1.489	5.3 (5.0-5.5)	1.294	4.2 (3.9-4.4)	5.341	18.9 (18.4-19.3)	7.194	23.1 (22.6-23.6)

*CI indicates confidence interval.

Asturias for children and in A Coruña, Asturias, and San Sebastián for adolescents. Similarly, the highest ORs for ever having had a diagnosis of asthma fell to children in Bilbao, Asturias, and A Coruña and to adolescents in San Sebastián, Bilbao, and A Coruña. Male sex was a risk factor for recent wheezing in children but not in adolescents. The self-reporting of having had a diagnosis of asthma also correlated with recent wheezing in both age brackets.

A linear correlation was found between the rates in each of the 2 age brackets by geographic areas for recent wheezing (coefficient of correlation, 0.72; *P*=.017) and asthma diagnosis (coefficient of correlation: 0.82; *P*=.003) (Figures 1 and 2). The figures also show that there is a group of areas where prevalences are higher than in other populations; those areas are Asturias, Bilbao, A Coruña, and San Sebastian.

Discussion

The Spanish ISAAC phase 3 study aimed to describe and analyze geographic variations in asthma in the country in order to establish the epidemiologic characteristics of the disease and facilitate the study of factors related to distribution in the area. The main finding of this study was to detect noteworthy geographic differences in the prevalence of asthma-related symptoms in the Spanish pediatric population, differences that adopted a coherent territorial pattern and were reflected in both age brackets (early childhood and early adolescence). Also of interest was the observation of considerable regional differences already evident in children aged 6-7 years along with evidence that those differences increased only slightly in adolescents aged 13-14 years. Those findings would

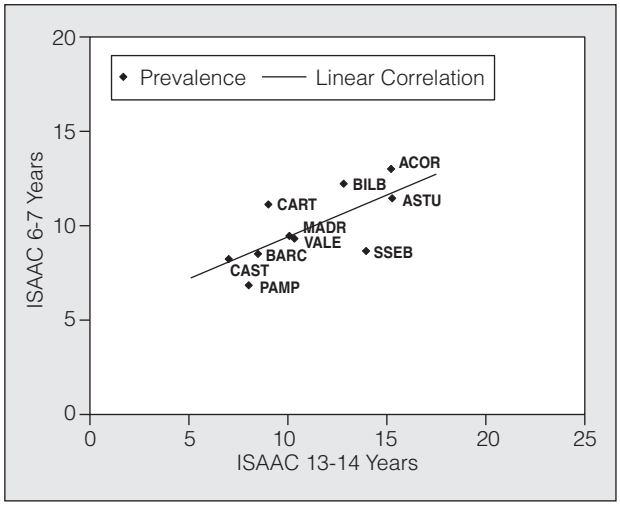

Figure 1. Correlation between recent wheezes (last 12 months) and age group (coefficient of correlation: 0.72; *P*=.017). ACOR indicates A Coruña; ASTU, Asturias; BILB, Bilbao; BARC, Barcelona; CART, Cartagena; CAST, Castellón; MADR, Madrid; VALE, Valencia; PAMP, Pamplona; and SSEB, San Sebastián.

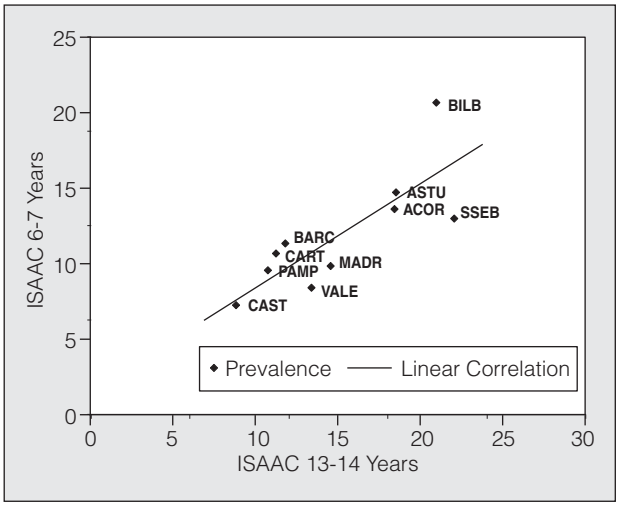

Figure 2. Correlation between ever having a diagnosis of asthma and age group (coefficient of correlation: 0.82; *P*=.003). ACOR indicates A Coruña; ASTU, Asturias; BILB, Bilbao; BARC, Barcelona; CART, Cartagena; CAST, Castellón; MADR, Madrid; VALE, Valencia; PAMP, Pamplona; and SSEB, San Sebastián.

TABLE 3
Prevalence of Ever Having Wheezes and Ever Being Diagnosed With Asthma (Written Questionnaire)*

	Ever Have Wheezes				Ever Have Asthma			
	6-7 Years		13-14 Years		6-7 Years		13-14 Years	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
A Coruña	1120	37.2 (35.5-38.9)	753	25.3 (23.7-26.9)	414	13.7 (12.5-15.0)	551	18.5 (17.1-20.0)
Asturias	984	32.6 (30.9-34.3)	766	25.8 (24.2-27.4)	446	14.8 (13.5-16.1)	554	18.6 (17.3-20.1)
Barcelona	688	23.8 (22.3-25.4)	494	17.8 (16.4-19.3)	324	11.2 (10.1-12.4)	331	11.9 (10.7-13.2)
Bilbao	999	33.0 (31.3-34.7)	609	21.2 (19.7-22.7)	626	20.7 (19.3-22.2)	608	21.1 (19.6-22.7)
Cartagena	899	33.2 (31.5-35.0)	556	19.5 (18.1-21.0)	293	10.8 (9.7-12.1)	324	11.4 (10.2-12.6)
Castellón	1.126	28.9 (27.4-30.3)	632	15.7 (14.6-16.9)	287	7.4 (6.6-8.2)	363	9.0 (8.2-10.0)
Madrid	726	31.1 (29.3-33.1)	520	19.7 (18.2-21.3)	232	9.9 (8.8-11.2)	375	14.2 (12.9-15.6)
Pamplona	717	22.7 (21.2-24.2)	354	12.2 (11.0-13.4)	305	9.6 (8.6-10.7)	317	10.9 (9.8-12.1)
San Sebastián	279	31.2 (28.2-34.4)	262	24.2 (21.6-26.8)	120	13.4 (11.3-15.8)	237	21.9 (19.4-24.4)
Valencia	1.015	30.1 (28.6-31.7)	741	23.8 (22.3-25.3)	286	8.5 (7.6-9.5)	422	13.5 (12.4-14.8)
Valladolid	—	—	407	13.9 (12.6-15.2)	—	—	365	12.4 (11.3-13.7)
Total	8.553	30.2 (29.7-30.8)	6.094	19.6 (19.1-20.0)	3.333	11.8 (11.4-12.2)	4.447	14.3 (13.9-14.7)

*CI indicates confidence interval.

TABLE 4
Logistic Regression Model: Estimation of the Odds Ratios (OR) for Recent Wheezing (Last 12 Months) by Geographic Area and Sex, Relative to the Geographic Area With the Lowest Prevalence and to Female Sex*

	6-7 Years				13-14 Years		
	OR	(95% CI)	*P*		OR	(95% CI)	*P*
Center				Center			
Pamplona	1.00			Castellón	1.00		
Castellón	1.19	(1.00-1.42)	.054	Pamplona	1.15	(0.96-1.38)	.127
Barcelona	1.20	(0.99-1.45)	.060	Valladolid	1.19	(0.99-1.42)	.057
San Sebastián	1.23	(0.94-1.61)	.135	Barcelona	1.22	(1.02-1.46)	.030
Valencia	1.37	(1.14-1.63)	.001	Cartagena	1.44	(1.21-1.71)	.000
Madrid	1.37	(1.13-1.66)	.002	Madrid	1.49	(1.25-1.77)	.000
Cartagena	1.65	(1.37-1.97)	.000	Valencia	1.54	(1.30-1.82)	.000
Asturias	1.71	(1.43-2.03)	.000	Bilbao	1.92	(1.63-2.26)	.000
Bilbao	1.83	(1.54-2.18)	.000	San Sebastián	2.13	(1.72-2.62)	.000
A Coruña	1.96	(1.65-2.33)	.000	Asturias	2.37	(2.03-2.77)	.000
				A Coruña	2.38	(2.04-2.79)	.000
Sex				Sex			
Female	1.00			Female	1.00		
Male	1.29	(1.19-1.40)	.000	Male	1.00	(0.93-1.07)	.950

*CI indicates confidence interval.

TABLE 5
Logistic Regression Model: Estimation of the Odds Ratios (OR) for Ever Having a Diagnosis of Asthma by Geographic Area and Sex, Relative to the Geographic Area With the Lowest Prevalence and to Female Sex*

	6-7 Years				13-14 Years		
	OR	(95% CI)	*P*		OR	(95% CI)	*P*
Center				Center			
Castellón	1.00			Castellón	1.00		
Valencia	1.21	(1.02-1.43)	.032	Pamplona	1.22	(1.04-1.44)	.013
Pamplona	1.34	(1.13-1.59)	.001	Cartagena	1.31	(1.12-1.53)	.001
Madrid	1.41	(1.18-1.69)	.000	Barcelona	1.39	(1.19-1.63)	.000
Cartagena	1.55	(1.30-1.84)	.000	Valladolid	1.43	(1.22-1.66)	.000
Barcelona	1.58	(1.33-1.86)	.000	Valencia	1.56	(1.35-1.82)	.000
San Sebastián	1.97	(1.57-2.47)	.000	Madrid	1.67	(1.43-1.94)	.000
A Coruña	2.05	(1.75-2.40)	.000	Asturias	2.32	(2.02-2.68)	.000
Asturias	2.22	(1.89-2.59)	.000	A Coruña	2.32	(2.01-2.67)	.000
Bilbao	3.33	(2.87-3.87)	.000	Bilbao	2.73	(2.38-3.15)	.000
				San Sebastián	2.84	(2.37-3.40)	.000
Sex				Sex			
Female	1.00			Female	1.00		
Male	1.29	(1.34-1.55)	.000	Male	1.30	(1.22-1.39)	.000

*CI indicates confidence interval.

indicate that geographic variations in asthma prevalence are largely established in early childhood.

The work for phase 3 of the Spanish arm of the ISAAC project was carried out at the same time as the work of other groups and used precise methodological protocols to investigate the prevalence of a series of asthma-like symptoms by way of a written questionnaire that is widely applied in the epidemiology of asthma.[3] Although the ISAAC phase 3 protocol included a video-assisted questionnaire about asthma symptoms for use with adolescents, only the written questionnaire was applied in the Spanish study to allow the same instrument to be used for both age brackets. A design issue to consider is that the questionnaire was filled in by an observer who was not the subject of investigation in some cases, depending on age. Nevertheless, there is sufficient evidence for agreement between the 2 ways of reporting given that the model filled in by parents and the one self-administered by adolescents are standardized and have been shown to have similar sensitivity and specificity in relation to the diagnosis of asthma supported by bronchial hyperreactivity tests.[10,14]

The ISAAC phase 3 study in Spain was carried out in areas selected by each group of local investigators and, therefore, study populations were not chosen randomly, a design feature that limits the extrapolation of the data to the whole country to a certain extent. Nevertheless, although this feature is considered a limitation, one that is inherent to the ISAAC method for all practical purposes, certain results deserve to be mentioned in connection with the country as a whole. The overall prevalence of recent wheezing, a basic reference for comparing asthma prevalence by country, was around 10% in both age brackets studied. That level is below average on an international scale of comparison.[4] Noteworthy is the scarce difference (less than a percentage point) between the prevalences for subjects in the 6-7-year-old and the 13-14-year-old age brackets. This suggests, in spite of limitations inherent to the cross-sectional nature of the study, that early childhood is when the incidence of asthma is most marked. Another aspect to emphasize is the high prevalence of recent wheezing with exercise in adolescents, a situation that has already been described as suggesting uncertainty about how the subjects are interpreting the question.[4] Another interesting finding is the low percentage answering that question affirmatively for children aged 6-7 years, possibly related to their parents' difficulty in perceiving such wheezing or to the lower intensity of physical exercise typical of that age. With regard to recent nocturnal symptoms, waking from wheezing was slightly more common in the younger children. Waking from nocturnal coughing, on the other hand, was common in children and particularly common in adolescents, again casting doubts on the specificity of that question.[4,10] The percentage of children with this symptom in the 6-7-year-old bracket was high, reaching nearly a third of the population. This was information that showed once again the extraordinarily high prevalence of respiratory disease with wheezing in the early years of life.[15] Finally, the prevalence of a self-report of ever having had asthma, indicating a medical diagnosis of that disease, was high for both children and adolescents. This finding means that it is highly unlikely that asthma is significantly underdiagnosed in Spain during the period of pediatric care.

The Spanish ISAAC phase 3 study involved 11 population centers on the peninsula (of which 10 included children in the age bracket of 6-7 years old). The centers can be grouped by geophysical characteristics as reflecting 3 general macro-regions: the northern Atlantic and Bay of Biscay coasts, the Mediterranean coast, and the interior. The first region is represented by A Coruña, Asturias, Bilbao, and San Sebastián, the second by Barcelona, Cartagena, Castellón, and Valencia, and the third by Madrid, Pamplona, and Valladolid. In the last population area, only adolescent subjects were studied. From this perspective, the analysis of geographic variation in the population areas that participated in the Spanish ISAAC phase 3 study showed clearly that children and adolescents on the northern Atlantic and Bay of Biscay coast have higher prevalences of asthma. First, the risk of presenting recent wheezing was clearly higher for both 6-7-year-old children and 13-14-year-old adolescents in that region, with the sole exception of the younger age bracket in San Sebastián. The risk of having ever had a diagnosis of asthma was even more markedly greater in that region, as shown by the findings for all 4 of the centers along that northwestern coastline. The combination of high prevalences of recent wheezes and a diagnosis of asthma for that region was also evident in the analysis of the correlation between results for the 2 age groups. Finally, the hypothesis that the corner of Spain bordering the northern section of the Atlantic coast and the Bay of Biscay has a relatively high prevalence of asthma is supported by an independent study carried out in the region of Cantabria, using the same method used in the ISAAC study.[16] That survey, based on a written questionnaire, analyzed the prevalence of asthma symptoms in 2253 adolescents in the age bracket of 13-14 years in the cities of Santander and Torrelavega in the same years as the present study (2001-2002) and reported rates of recent wheezing that are nearly identical to those we observed for the northwestern coast. However, although the study of population centers in the Spanish ISAAC phase 3 study has allowed us to define a characteristic geographic pattern with precision, we are still far from having a complete picture of the distribution of asthma in the country, given that the method applied has the evident limitation of lack of data for many areas, particularly the coastal and interior parts of the southern portion of peninsular Spain as well as for the Balearic and Canary Islands. In this respect, it is important to remember the high prevalence of asthma in adolescents in Cádiz found

during the first phase of the ISAAC study in Spain. This means we must consider that the high prevalences detected for the northern Atlantic and Bay of Biscay coasts might also be found along other parts of the Spanish coastline.

Variations in Spain in the prevalence of symptoms related to asthma (2-fold higher in some areas than in others) raises questions about the nature of the contributing factors. We must bear in mind that analyses of smaller areas carried out in other countries have found that there is little variation, probably because the national populations in those countries share risk.[17-21] Although a genetic contribution can not be ruled out in Spain altogether, particularly because differences in immigration patterns across the country might play a role,[22] climate-related factors are candidates for consideration through an influence on the distribution of perennial and seasonal allergens[23] or their role in modulating the long-term impact of acute viral infections characteristic of the period of childhood growth.[24] On the other hand, the factors that are usually linked to the hygiene hypothesis for asthma—such as the number of children and birth order, socioeconomic level and other characteristics that affect the incidence of bacterial and viral infections while the immune system is immature[25]—are uniformly distributed in Spain and there is no apparent geographic variation that might support the hypothesis. Likewise, for similar reasons, it also seems unlikely that differences in environmental pollution or exposure to tobacco smoke during gestation or after birth are responsible for the geographic variation observed in this study. In any case, whatever the contributing factors might be, it seems clear that they play a role early in childhood, a moment on which we should concentrate our research efforts in the form of cohort studies. Such studies will allow clarification of the beginning of the natural history of the asthmatic process[26] as well as the identification of factors related to persistence of the disease at later stages of life.[27,28]

In summary, this study of the geographic distribution of asthma symptoms has shown that at the beginning of the present decade the prevalence of recent wheezing in Spain was around 10% for both early childhood and early adolescence, although there was considerable variation from region to region. An area of relatively high prevalence has been identified. It consists of the communities along the northern Atlantic coast and the Bay of Biscay. Differences are less precisely defined along the Mediterranean coast and the interior of the peninsula, both of them regions where the prevalences of symptoms are lower. Finally, this study has shown that the geographic differences in the prevalence of asthma symptoms appear early, indicating that the search for causes should concentrate on the first stages of life.

APPENDIX

Asthma Symptoms Questionnaire (6-7 years/13-14 years) of the International Study of Asthma and Allergies in Childhood (ISAAC)

1. Have you (has your child) ever had wheezing or whistling in the chest at any time in the past?
   Yes No

2. Have you (has your child) had wheezing or whistling in the chest in the last 12 months?
   Yes No

3. How many attacks of wheezing have you (has your child) had in the last 12 months?
   None 1-3 4-12 >12

4. In the last 12 months, how often on the average, has your sleep (has your child's sleep) been disturbed due to wheezing?
   Never woken with wheezing Less than 1 night per week 1 or more nights per week

5. In the last 12 months, has wheezing ever been severe enough to limit your (your child's) speech to only one or two words at a time between breaths?
   Yes No

6. Have you (has your child) ever had asthma?
   Yes No

7. In the last 12 months, has your (your child's) chest sounded wheezy during or after exercise?
   Yes No

8. In the last 12 months, have you (has your child) had a dry cough at night apart from a cough associated with a cold or flu?
   Yes No

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