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# ORIGINAL ARTICLE



# Prevalence of symptoms, severity and diagnosis of asthma in adolescents in the Province of Salamanca, Spain: Global Asthma Network (GAN) Phase I

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# **KEYWORDS**

adolescents; asthma; GAN; ISAAC; prevalence

#### Abstract

Introduction and objectives: Asthma is the most prevalent chronic disease in childhood. However, the latest data on its prevalence in Spain are from Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC), 2004. The objective of our study was to assess the prevalence of asthma symptoms, severity and diagnosis in the paediatric population aged between 13 and 14 years in the province of Salamanca.

Material and methods: Cross-sectional multicentre study carried out in 2017-2018 in 13and 14-year-old school children in the province of Salamanca as a centre participating in of the Global Asthma Network (GAN) Phase I. The standardised validated written questionnaire and that directed by a video was administered; it was self-completed by the pupils. Results: A total of 3485 questionnaires were completed, and the pupils' participation rate was 95.01%. Among the total, 25.7% indicated having had wheeze ever (20.7% in the video questionnaire); 14.7% indicated having had wheeze in the past 12 months (11.3% in the video questionnaire). The prevalence of current wheeze that limited speech was 3.9% (7.5% in the video questionnaire) and the current prevalence of severe wheeze was 6.5%. Regarding asthma diagnosis, 19.7% of the sample answered that they had had asthma ever, whilst 14.0% referred to having physician-diagnosed asthma. The agreement between the written questionnaire and that directed by video was acceptable for the questions of wheeze ever (Cohen Kappa index [k] = 0.53) and current wheeze (k = 0.42).

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Conclusions: The prevalence of current asthma (wheeze in the past 12 months) in the population aged 13 and 14 years in the province of Salamanca is higher compared with that presented in 2004 in Spain, but similar to that described at the world level (low-moderate level), according to the ISAAC Phase III studies.

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#### Introduction

Asthma is the most prevalent chronic disease in childhood affecting over 339 million people throughout the world, supposing a major clinical and public health problem, with a constant burden on national health systems. One of the main concerns is its elevated mortality majority of which are preventable, amounting to around 1000 deaths per day.<sup>1,2</sup>

Epidemiological studies have been developed to determine the prevalence of asthma in the world; based on the self-reporting of symptoms related to asthma using standardised questionnaires.<sup>3-5</sup> The complete information about the prevalence and impact of certain environmental factors on asthma in infants and adolescents and their comparison in different countries of the world has been provided by the International Study of Asthma and Allergies in Childhood (ISAAC) carried out in three phases between 1992 and 2004.<sup>6</sup>

The study by García-Marcos et al. reported that the prevalence of asthma in Spain amongst children aged between 13 and 14 years was approximately 10% and remained stable throughout the study period 1992-2004.<sup>7</sup> Besides genetic predisposition, which can vary depending on different populations, social and environmental factors also cause variations in the prevalence depending on the geographic area measured.<sup>8</sup> Variations in the prevalence and severity of asthma have been documented in different regions and countries of the world since the first ISAAC global report.<sup>9</sup> The prevalence of asthma at an international scale was 14.1% in the early 2000s.<sup>6</sup>

The influence of sex has likewise been seen in the prevalence of wheeze/asthma, being more frequent in boys than in girls and vice versa during the adult stages.<sup>10</sup>

For improving and extending the ISAAC, the Global Asthma Network (GAN) was established in 2012, based on the focus and methods of ISAAC including the global vigilance of asthma prevalence, severity, management and risk factors.<sup>11</sup>

In the first phase of the 13- and 14-year-old age group GAN (2015-2020), 63 centres in 25 countries have sent their data to the coordinating centres, whose data quality and methodology is being analysed. Five centres in Spain have completed this first phase (Cartagena, Salamanca, Cantabria, A Coruña and Pamplona), although data from those centres are yet to be published.<sup>12</sup> The participation of Spain in GAN Phase I will enable one to know the asthma prevalence trends concerning the last 20 years at both world and national level. The interest of the Salamanca

centre in participating in the study also lies in knowing the first-hand information of sophistication in this area that would enable us to establish comparisons with the surrounding areas and better understand the epidemiology and burden of asthma, and its management in the adolescents of the said population.

The objective of this article is to assess the prevalence of symptoms, severity, and diagnosis of asthma in the paediatric population aged 13-14 years in the province of Salamanca.

# Materials and Methods

# Study design

This study is a multicentre epidemiological study whose fieldwork was performed in the school setting between March 2017 and April 2018 in the province of Salamanca as a centre participating in the international GAN Phase I. Details of the GAN methodology, along with its corresponding manual, is available from http://globalasthmanetwork.org/surveillance/manual/methods.php and in a recent publication.<sup>13</sup>

# Study population

GAN Phase I recommends a sample of at least 3000 participants to achieve a modest estimation of the prevalence. A total of 45 schools in the province of Salamanca were randomly selected; 31 of them agreed to participate, with a total attendance of 3668 pupils between 13 and 14 years. The study was carried out in the pupils' classrooms with questionnaires filled out by the pupils themselves.

# Ethics committee approval

The Ethics Committee for Clinical Research of the Salamanca Health Area approved GAN Phase I in the province of Salamanca (GRS 1239/b/16). Passive informed consent was obtained from all the participants.

# Questionnaire

GAN Phase I uses the same standardised and validated questionnaire developed for the ISAAC study of asthma symptoms and adds the physician-confirmed diagnosis of

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asthma, allergic rhinitis and atopic dermatitis. The questionnaire has been translated from English to Spanish and back translated to ensure to retain the original sense.

The questionnaire used in the present study was the same as the one used in GAN Phase I. Its Spanish version was used in the coordinating centre for Spain (Cartagena), which can be accessed from http://pediatria.imib.es/portal/instituto/pediatria\_gan.jsf. No modification was made to this version.

The questionnaire gathers the demographic data and includes sections referring to symptoms related to asthma, severity in the participants, consumption of resources, risk and/or protective factors and medication used.

Additionally, the pupils completed a questionnaire directed by video translated into Spanish, which can also be accessed from the previous link. The video presents five individuals of different ages with asthma episodes of greater or lower intensity in varied contexts.

The questionnaires were coded employing an identification code for each participant that specified the Salamanca centre and their school.

#### Main variables

The question of a wheezing attack in the last 12 months ("current wheeze") was chosen as the primary variable for the current prevalence of wheeze assessment, since this was the most useful question for establishing the prevalence of wheeze to reduce recall bias by limiting it to a period of 12 months, in the ISAAC study. The accumulated prevalence of wheeze was determined using the question: "Have you ever had whistling in the chest?" A new variable, "current severe wheeze," defined as wheezing in the past 12 months with a frequency  $\geq 4$  episodes or had caused  $\geq 1$  wakening at night per week or had limited speech was created from other questions on the frequency and severity of symptoms to evaluate asthma severity.

Variables related to the current asthma diagnosis, such as whether they had ever had asthma (prevalence of asthma diagnosis) and if that diagnosis had been confirmed by a physician (prevalence of confirmed asthma diagnosis), were also gathered.

# Implementation of the study

The study was carried out in the school classroom. A written questionnaire was handed in, and the video questionnaire was shown so that the pupils could self-complete the questionnaires, in 60-90 min. The entire process was invigilated by a trained research team, and the pupils were invited to clear their doubts. Words that could induce answers, such as "asthma," were not to be mentioned.

# Statistical analysis

The self-completed questionnaires were sent to the coordinating centre (Murcia, Optical Mark Recognition system) where the data was exported to an Excel spreadsheet. A descriptive analysis of all the variables, providing the

prevalence of symptoms, severity and asthma diagnosis was carried out for the total sample stratified by sex (95% confidence interval [CI]).

Following the recommendations in the GAN manual, unanswered and incorrectly answered responses to the questionnaire were included in denominators of the prevalence. Associations have been determined among the different qualitative variables of the questionnaires with sex using the Chi-squared test. The percentage of coinciding cases that answered yes and their 95% CI and the Cohen Kappa index (k) were calculated for the total sample stratified by sex to evaluate the agreement between the prevalence of the written questionnaire and that directed by video. The significance level was set to 5% (p < 0.05). All the analyses were performed using the statistical software IBM SPSS Statistics for Windows, version 26 (IBM, Armonk, NY, USA).

#### Results

Among the 3668 possible participants, 183 declined to participate. So, the participation rate was 95.01%, with 50.9% girls.

# Written questionnaire

The prevalence of asthma symptoms and their severity stratified by sex was presented globally (Table 1). The accumulated prevalence of wheeze (wheeze ever) was 25.7% (95% CI, 24.2-27.2), whereas the current wheeze prevalence (wheeze in the past 12 months) was 14.7% (95% CI, 13.5-15.9). The accumulated prevalence of wheeze was higher in girls compared with boys (27.7% vs. 23.6%; P = 0.007). The prevalence of current severe wheeze (current refers to the past 12 months) was 6.5% (95% CI, 5.7-7.3). The prevalence of a diagnosis of asthma answered having had asthma at some time was 19.7% (95% CI, 18.4-21.0), whereas 14.0% referred to a physician-confirmed asthma diagnosis (95% CI, 12.8-15.2).

The prevalence of current wheeze during exercise and night-time cough also showed significant differences, being higher in girls than in boys in both cases (28.2% vs. 18.8%; 33.6% vs. 23.3%, respectively).

Concerning health care, statistically significant differences were found in the number of recent visits: a greater prevalence was found for 1-3 visits in girls than in boys for unscheduled visits to the doctor (10.9% vs. 8.2%), and a greater prevalence of 1-3 visits to the emergency department not requiring hospitalisation (6.2% vs. 4.4%).

# Video questionnaire

The positive answers to the video-directed questionnaire are presented as the total of the sample stratified by sex (Table 2). Of the five situations in the video questionnaire, the accumulated asthma prevalence was 20.7% (95% CI, 19.4-22.0), whilst the prevalence of current asthma was 11.3% (95% CI, 10.2-12.4%). As for the prevalence of current severe wheeze, 7.5% of the sample answered yes (95% CI, 6.6-8.4%). For the presence of current night-time symptoms that woke them at night, 18.2% answered that they had had night-time cough (95% CI, 16.9-19.5%), whereas 4.4%

Table 1	Prevalence and severity	of asthma sympton	ms and asthma diagnosis	of the sample, stratified by	/ sex.a

	Total (n = 3485)			(	Girls (n =	1751)	В	Р		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	value
Wheeze ever	896	25.7	24.2-27.2	485	27.7	25.6-29.8	399	23.6	21.6-25.6	0.007
Current wheezeb	511	14.7	13.5-15.9	291	16.6	14.9-18.3	213	12.6	11.0-14.2	0.066
Current whistling episodes										0.018
None	148	4.2	3.5-4.9	75	4.3	3.3-5.3	69	4.1	3.2-5.0	
1-3	343	9.8	8.8-10.8	194	11.1	9.6-12.6	144	8.5	7.2-9.8	
4-12	108	3.1	2.5-3.7	71	4.1	3.2-5.0	36	2.1	1.4-2.8	
>12	37	1.1	0.8-1.4	14	0.8	0.4-1.2	22	1.3	0.8-1.8	
Night-time whistling										0.039
Never	403	11.6	10.5-12.7	215	12.3	10.8-13.8	184	10.9	9.4-12.4	
<1 night/week	181	5.2	4.5-5.9	111	6.3	5.2-7.4	66	3.9	3.0-4.8	
≥1 night/week	36	1.0	0.7-1.3	24	1.4	0.8-2.0	10	0.6	0.2-1.0	
Current wheeze that limits speech	137	3.9	3.3-4.5	86	4.9	3.9-5.9	48	2.8	2.0-3.6	0.051
Current severe wheeze <sup>c</sup>	228	6.5	5,7-7,3	134	7.7	6,5-8,9	89	5.3	4,2-6,4	< 0.001
Current wheeze during exercise	825	23.7	22.3-25.1	493	28.2	26.1-30.3	318	18.8	16.9-20.7	<0.001
Current night-time cough	997	28.6	27.1-30.1	588	33.6	31.4-35.8	394	23.3	21.3-25.3	< 0.001
Asthma ever	665	19.7	18.4-21.0	320	18.3	16.5-20.1	334	19.8	17.9-21.7	0.367
Physician-diagnosed asthma	489	14.0	12.8-15.2	235	13.4	11.8-15.0	245	14.5	12.8-16.2	0.126
Number of recent unschedule visits to the doctor	ed									0.044
None	2988	85.7	84.5-86.9	1487	84.9	83.2-86.6	1463	86.7	85.1-88.3	
1-3	335	9.6	8.6-10.6	191	10.9	9.4-12.4	138	8.2	6.9-9.5	
4-12	45	1.3	0.9-1.7	23	1.3	0.8-1.8	22	1.3	0.8-1.8	
>12	17	0.5	0.3-0.7	6	0.3	0.0-0.6	10	0.6	0.2-1.0	
Number of recent visits to emergency department without hospitalisation										0.021
None	3182	91.3	90.4-92.2	1602	91.5	90.2-92.8	1541	91.3	90.0-92.6	
1-3	189	5.4	4.6-6.2	108	6.2	5.1-7.3	75	4.4	3.4-5.4	
4-12	22	0.6	0.3-0.9	8	0.5	0.2-0.8	14	0.8	0.4-1.2	
>12		0.5	0.3-0.7	5	0.3	0.0-0.6	12	0.7	0.3-1.1	
Number of recent hospitalisations										0.282
None	3286	94.3	93.5-95.1	1668	95.3	94.3-96.3	1576	93.4	92.2-94.6	
1	77	2.2	1.7-2.7	37	2.1	1.4-2.8	38	2.3	1.6-3.0	
2	29	0.8	0.5-1.1	12	0.7	0.3-1.1	16	0.9	0.4-1.4	
>2	14	0.4	0.2-0.6	4	0.2	0.0-0.4	10	0.6	0.2-1.0	

<sup>a</sup>In the sample there were 46 instances of data lost for the variable of sex, so the sum of the two columns of each stratum is not the same as the column of the totals.

referred to having had sleeping disorders because of the wheeze (95% CI, 3.7-5.1%).

# Agreement between the written questionnaire and video questionnaire

The agreement between the equivalent questions in the written and the video questionnaire was analysed (Table 3).

A moderate agreement for the question of wheeze ever  $(\kappa=0.54;~95\%~\text{Cl},~0.49\text{-}0.58)$  and current wheeze  $(\kappa=0.42;~95\%~\text{Cl},~0.32\text{-}0.52)$  needs to be highlighted. A greater prevalence of agreement between both questionnaires was observed in girls than in boys, with statistically significant differences for the variables of wheeze with exercise and night-time cough, of up to 4.9 percentage points for the girls (P < 0.01) and for wheeze that limits speech, which was double in the girls (P = 0.018).

bRefers to the past 12 months.

<sup>&</sup>lt;sup>c</sup>Refers to those who answered to having asthma in the past 12 months:  $\geq$  4 episodes or  $\geq$  1 waking up at night/week due to wheeze or wheeze that limited speech.

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Table 2 Prevalence and asthma symptoms according to the video questionnaire in 13-14 year old adolescents by sex.

	Total (n = 3485)			(	Girls (n :	= 1751)	E	P value		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	
Ever										
Wheeze at rest	721	20.7	19.4-22.0	379	21.6	19.7-23.5	334	19.8	17.9-21.7	0.166
Wheeze with exercise	1000	28.7	27.2-30.2	552	31.5	29.3-33.7	435	25.8	23.7-27.9	< 0.001
Night-time wheeze	345	9.9	8.9-10.9	184	10.5	9.1-11.9	154	9.1	7.7-10.5	0.170
Night-time cough	1022	29.3	27.8-30.8	590	33.7	31.5-35.9	419	24.8	22.7-26.9	< 0.001
Wheeze that limits speech	480	13.8	12.7-14.9	270	15.4	13.7-17.1	204	12.1	10.5-13.7	0.004
In the past 12 months										
Wheeze at rest	394	11.3	10.2-12.4	223	12.7	11.1-14.3	166	9.8	8.4-11.2	0.034
Wheeze with exercise	657	18.9	17.6-20.2	377	21.5	19.6-23.4	271	16.1	14.3-17.9	0.034
Night-time wheeze	155	4.4	3.7-5.1	86	4.9	3.9-5.9	66	3.9	3.0-4.8	0.431
Night-time cough	636	18.2	16.9-19.5	386	22.0	20.1-23.9	242	14.3	12.6-16.0	0.040
Wheeze that limits speech	262	7.5	6.6-8.4	163	9.3	7.9-10.7	96	5.7	4.6-6.8	0.001
In the past month										
Wheeze at rest	164	4.7	4.0-5.4	87	5.0	4.0-6.0	75	4.4	3.4-5.4	0.484
Wheeze with exercise	300	8.6	7.7-9.5	166	9.5	8.1-10.9	121	7.8	6.5-9.1	0.857
Night-time wheeze	66	1.9	1.4-2.4	40	6.1	5.0-7.2	24	1.4	0.8-2.0	0.079
Night-time cough	200	5.7	4.9-6.5	137	7.8	6.5-9.1	59	3.5	2.6-4.4	0.001
Wheeze that limits speech	120	3.4	2.8-4.0	69	3.9	3.0-4.8	49	2.9	2.1-3.7	0.855

**Table 3** Agreement between equivalent questions from the written and the video questionnaire in 13-14 year old adolescents by sex.

			Total		Girls					Boys				
	n	%	к	95% CI	n	%	κ	95% CI	n	%	κ	95%CI		
Wheeze ever	517	14.8	0.54	0.49-0.581	270	15.4	0.51	0.45-0.57	241	14.3	0.56	0.50-0.63	0.329	
Current wheeze	251	7.2	0.42	0.33-0.52	142	8.1	0.38	0.24-0.52	107	6.3	0.47	0.34-0.61	0.154	
Wheeze with exercise	442	12.7	0.23	0.16-0.23	264	15.1	0.17	0.07-0.27	173	10.2	0.29	0.19-0.39	<0.001	
Night-time wheeze	72	2.1	0.19	0.04-0.33	41	2.3	0.16	-0.04-0.36	29	1.7	0.23	0.02-0.44	0.490	
Night-time cough	376	10.8	0.12	0.05-0.19	229	13.1	0.08	-0.01-0.17	141	8.4	0.16	0.06-0.26	< 0.001	
Wheeze that limits speech	57	1.6	0.13	0.01-0.26	38	2.2	0.15	-0.01-0.31	17	1.0	0.05	-0.15-0.26	0.018	

n, number of cases coinciding with affirmative answers in the written and the video questionnaire.

#### Discussion

The results of this study showed a prevalence of current wheeze of 14.7%, based on the written questionnaire; compared with the global prevalence of ISAAC Phase III studies in 2004 for the 13-14 year old age group it is similar to that described at the international level (14.1%).6 However, this figure is slightly higher than the overall prevalence at the national level (10.6%) and extremely higher compared with that found at local level in the province of Valladolid (8.2%). No differences between sexes were found in the present-day prevalence of current wheeze, as was the case described in ISAAC Phase III in Spain.14 In the ISAAC study, the presence of current wheeze (having wheeze in the past 12 months) was the main variable for comparing the asthma prevalence among countries, since in the prior validation studies it obtained a better correlation with the current asthma prevalence, probably by reducing recall bias.3

The primary chosen variable regarding asthma severity was current severe wheeze; its definition was the same as in the previous ISAAC studies (having had, in the past 12 months:  $\geq 4$  episodes, or  $\geq 1$  night-time wakening/week, or speech-limiting wheeze). The prevalence in our study (6.5%) was like the global prevalence described in Phase III at the world level (6.9%), but considerably higher than that presented in Spain and Valladolid (around 4%) in 2004.9 The current severe wheeze, night-time cough and wheeze symptoms were higher in girls.

The prevalence of an asthma diagnosis (19.7%) had increased considerably both at international (12.6%) and national levels (13.9%). Confirmed physician-diagnosed asthma was lower compared with having ever had asthma. Concerning that current wheeze remained stable at the international level, indicating that asthma was increasingly better diagnosed, although its medical confirmation is lesser than that desirable.

The definition of asthma has presented wide heterogeneity in cohort studies carried out on infants.<sup>15</sup> Asthma has a broad clinical spectrum, ranging from a minute or even asymptomatic to major and life-threatening forms. Hence, it is considered as a syndrome rather than a disease, in which patients with recurring symptoms caused by variable airway obstruction, such as wheeze, cough, shortness of breath or thoracic oppression that varies over time and in intensity, are grouped together.<sup>17</sup>

Questionnaires are a critical tool for gathering clinical data as they are cost-effective and provide the patient's perspective themselves. However, they may present problems in the diagnostic process as they generate a broad variability in the perception of symptoms because of self-selection and recall biases. The sensitivity and specificity are not elevated, and hence other complementary studies such as measuring bronchial hyperresponsiveness (BHR) are required, which presents a high specificity albeit with low sensitivity. Nevertheless, the validity of questionnaires seems to be reasonably demonstrated as they have been compared with BHR measurements to establish an asthma diagnosis without having shown a diagnostic superiority for epidemiological studies with the use of complementary tests.

This study, performed following the standardised GAN methodology<sup>19,20</sup> similar to that designed for the ISAAC Phase III study,<sup>21</sup> enabled us to analyse the prevalence of different asthmatic symptoms (wheeze at rest, with exercise, at night; night-time cough), their severity (current severe wheeze, speech-limiting wheeze, unscheduled visits to their doctor or the Emergency Department as well as the hospitalisation rate due to asthma symptoms) and the prevalence of an asthma diagnosis for the first time in the province of Salamanca, through self-completed questionnaires.

The pupil participation rate in Salamanca was very satisfactory (95.01%) and slightly higher than the global rate described in Phase III for our country (88.5%).<sup>14</sup> The similarity in the participation rate and the use of the same methodology allowed us to assume that the prevalence obtained are comparable with previous studies that used the same methodology.<sup>22</sup>

The agreement between the written and the video questionnaire was moderate concerning the current wheeze and wheeze ever and weak for the rest of the questions, similar to that described in previous studies.<sup>23,24</sup>

The Salamanca centre is the first to publish its data about GAN Phase I in Spain. It would be interesting to collect the data from the surroundings centres in the same timeframe for comparison. This study will aid to know the global trend of asthma in Spain over the past 20 years.

The present study has some limitations. It is a cross-sectional study of the school-setting population. Because of frequent exams and the holiday, the pupil's fieldwork took 1 year, although at least half of the data collection was carried out in the pollen season, as recommended.<sup>19</sup> In this study, as in Phases I and III of the ISAAC study, objective disease measurements are not available, so evaluation of asthma symptoms depends exclusively on the pupils' perceptions. However, the strengths of the study that can be highlight are: we obtained a high participation rate which was able to recruit a sample of 3485 subjects, a number

above the recommended minimum, and additionally the application of a standardised methodology which enabled us to know, for the first time in this region, the epidemiology of asthma in its adolescents and be able to compare with that of its surroundings and at world level.

#### **Conclusions**

The prevalence of current and severe wheeze in the province of Salamanca is moderate and seems to have remained stable concerning that described in ISAAC Phase III at the international level but is higher than that found in Spain in the same period. In general, the total prevalence of the questions were lower in the video questionnaire compared with those in the written questionnaire, and agreement was minimal.

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# Conflict of Interest

No potential conflicts of interests with respect to the research, authorship and/or publication of this article was reported by the authors.

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