



ORIGINAL ARTICLE

Study of wheezing and its risk factors in the first year of life in the Province of Salamanca, Spain. The EISL Study[☆]

J. Pellegrini-Belinchón^{a,*}, G. Miguel-Miguel^a, B. De Dios-Martín^a, E. Vicente-Galindo^b, F. Lorente-Toledano^c, L. García-Marcos^d

^a Primary Care Paediatricians, Salamanca, Spain

^b Department of Statistics, University of Salamanca, Spain

^c Department of Pediatrics, University of Salamanca, Spain

^d Department of Pediatrics, University of Murcia, Spain

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Summary

Objectives: To determine the prevalence of wheezing and its associated risk factors in infants in the first year of life in the province of Salamanca, Spain.

Methods: A multicentre, cross-sectional, descriptive epidemiological study was designed to evaluate a representative sample of 750 infants in the first year of life, born in the province of Salamanca between 1 June 2008 and 30 September 2009.

The study was based on a previously validated and standardised written questionnaire administered among the parents of those children seen for control at 12 months of age in any of the Primary Care centres in the province of Salamanca.

Results: The recorded wheezing rate was 32.3%. Feeding and sleep were seen to be affected in 46.3% and 80.9% of the wheezing children, respectively, and parent activity was also altered in 39.3% of the cases.

A relationship was found between wheezing and nursery attendance (OR: 1.66, 95% confidence interval [1.19–2.31]); weight at birth >3500 g (OR: 1.45 [1.02–2.06]); the presence of eczema at this age (OR: 2.72 [1.75–4.24]); exclusive breastfeeding for <3 months (OR: 1.33 [0.98–1.81]); and maternal smoking during the last three months of pregnancy (OR: 1.60 [0.96–2.68]).

The prevalence of recurrent wheezing (defined as three or more episodes) was 11.9%. Significant differences were observed with respect to nursery attendance (OR: 1.71 [1.08–2.72]), the presence of eczema at this age (OR: 2.55 [1.48–4.42]), a history of maternal asthma (OR: 2.19 [1.08–4.44]) and exclusive breastfeeding for <3 months (OR: 1.53 [0.98–2.38]).

Conclusions: In the province of Salamanca, one third of the infants studied suffered wheezing in the first year of life. Infants exclusively breastfed for less than three months; attending a nursery; having suffered eczema; or with an asthmatic mother showed significantly more wheezing than the rest. Wheezing proved recurrent in 11.9% of the cases.

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[☆] International study of wheezing in infants, Primary Care centres of the province of Salamanca, Spain.

* Corresponding author.

E-mail address: jpellegrini@wanadoo.es (J. Pellegrini-Belinchón).

Introduction

Wheezing is one of the most common causes of consultation in Paediatrics and of hospital admission in the first years of life. Recurrent wheezing has a significant impact upon the quality of life of patients and their families,¹ with an important increase in healthcare resource utilisation and a high economical cost.

In 1992, the International Study of Asthma and Allergies in Childhood (ISAAC) made use of a simple methodology to conduct an epidemiological survey of such disorders.² The ISAAC, in its phases I, II and III, has contributed the first large-scale data on asthma in children, offering very useful epidemiological information on this disease in large parts of the world, referring to children between 6 and 7 years of age and adolescents between 13 and 14 years of age.

While the prevalence and risk factors of asthma have been well studied in older children, and although different cohort studies conducted from birth have shed abundant light on the origin of wheezing in the first months and years of life,³ it is suspected that infants under one year of age show a high prevalence and incidence of wheezing episodes, and that there are different subgroups which express different inflammatory responses to a range of triggering agents. However, there are hardly any studies in this age segment. As a result, in recent years studies have been developed specifically addressing this infant population and focusing on viral aetiology⁴; allergic influences⁵; obstetric antecedents⁶; early exposure to certain allergens; environmental exposures⁷; or the use of certain drug substances during pregnancy.

It thus seems necessary to conduct broad multicentre studies involving a simple methodology, designed to determine and compare the prevalence of wheezing in nursing infants in the first year of life, and to evaluate the risk factors which might favour the presence of wheezing in this age range. Such studies moreover would pave the way for future research on the aetiology and evolution of the prevalence of the disorder in relation to different influencing genetic, environmental, lifestyle and medical care factors.

The present study has been carried out following the standardised method of the International study of wheezing in infants (EISL), based on a validated questionnaire⁸ and involving a very large sample of infants under one year of age in Latin America, Spain and the Netherlands.⁹

Materials and methods

The study was carried out using the aforementioned EISL questionnaire. Validation of the questionnaire in Spain was carried out,⁸ and its performance in terms of sensitivity, specificity and positive and negative predictive value is equivalent to that of other questionnaires in reference to objective testing.¹⁰ The methodology used in the EISL is based on that employed in the ISAAC in its phases I and III in older children.² The mentioned questionnaire is the basis of the EISL, of which this study in Salamanca, Spain forms part, and includes questions on wheezing in the first year of life and on the associated risk and/or protective factors.

The study was approved by the Ethics Committees of Salamanca.

Design

This is a multicentre, cross-sectional, descriptive epidemiological study designed to evaluate a representative sample of 750 infants in the first year of life, born in the province of Salamanca between 1 June 2008 and 30 September 2009.

Study subjects

The questionnaire was delivered to the parents of the children visiting the Primary Care centres in the province of Salamanca on occasion of the programmed control at 12 months of age. Those infants whose parents failed to complete the questionnaire were excluded from the study, as were those presenting incomplete or incorrectly completed questionnaires, cases in which the number of wheezing episodes in the first year could not be specified, and cases where written informed consent was not obtained.

Definitions

Wheezing was considered to have occurred when receiving a positive reply to the question: "Has your child experienced wheezing or whistling in the chest in the first 12 months of life?" Recurrent wheezing (RW) was defined as three or more episodes in the first year of life.

Infant eczema was recorded when receiving a positive reply to the question: "Has your child suffered red spots on the skin that itch and which appear and disappear anywhere on the body except around the mouth and nose, and in the area of the nappy?"

Likewise, colds were recorded when receiving a positive reply to the question: "Has your child suffered episodes of sneezing, cough and runny nose with or without fever?"

Asthma and rhinitis were defined as either parent presenting the disease according to personal description.

Variables

The primary study variable was the presence or absence of wheezing during the first year of life. Wheezing and RW have been used as dependent variables in the association study. Variables related to wheezing were documented, such as the number of episodes; age at onset; relation to physical exercise, laughing or crying; impact upon patient feeding or sleep, or parent activities; changes in family life; treatments received; visits to the Emergency Department; diagnosis of asthma; relation to eczemas; and severity. In addition, data were collected in relation to risk or protective factors such as gender; weight and height at birth and at one year of age; race or ethnic group; place of birth; mother smoking during pregnancy or in either parent after birth; family antecedents of asthma, rhinitis, eczema or allergic diseases; exclusive breastfeeding; age at time of the first cold; nursery attendance; presence of pets in the home at the time of birth and during the first year of life of the infant; educational level of the parents; and home living conditions, such as the presence of carpeting or humidity (dampness).

Statistical analysis

The questionnaires were digitalised by a scanner (Fujitsu M4097D) using the Remark Office OMR version 6 program (Principia products, Paoli, PA, USA).

Frequencies and percentages were calculated for the descriptive study of qualitative variables. The mean and standard deviation were calculated in the case of quantitative variables. Statistical significance in comparing qualitative variables was evaluated with the chi-squared test. Relationships between qualitative and quantitative variables were explored with the Student *t*-test or analysis of variance (ANOVA), as applicable. Statistical significance was considered for $p < 0.05$. The SPSS version 16.0 statistical package was used throughout. Odds ratios (ORs) with their corresponding confidence intervals and *p*-values were calculated using an application developed from Microsoft Excel 2007.

Results

A total of 750 children (394 males, 52.5%) with a mean weight at birth of 3.03 kg (SD = 0.77) and a height of 49.48 cm (SD = 3.46) were studied. Table 1 shows the descriptive results of the sample. Mean maternal age at the time of birth of the infant was 33.64 years (SD = 4.61).

The prevalence of wheezing was 32.3%. Of the 242 children with wheezing in the first year of life, 90 suffered a single episode; 68 had two episodes; and 89 suffered three or more episodes. The prevalence of RW was 11.9%.

A total of 65.8% of the children with wheezing experienced the latter in the first six months of life, while 81.4% did so in the first eight months. The mean age at the time of the first wheezing episode was 4.79 months (SD = 3.21), and the age interval in which first wheezing was most frequently recorded was 4–6 months (Fig. 1).

Table 2 presents the descriptive results of the children with antecedents of wheezing. Almost one-half of the interviewed parents considered wheezing to interfere with the feeding of their infants, and in four out of every 10 cases the parent's activities were limited because of the disorder. Although sleep was affected in 80% of the children, frequent awakening was only recorded in 6.2% of the cases. Of the 242 children with wheezing, 112 required emergency care and 21 were admitted to hospital. Four of these infants required two or more admissions.

Tables 3 and 4 show the results of the associations between the different study variables with respect to

Table 1 Study subjects. Descriptive results.

	<i>n</i>	%
<i>Infants studied</i>		100
<i>Males</i>	394	52.5
<i>Race</i>		
Caucasian	727	96.9
Latin American (Indian)	7	0.9
Gypsy	10	1.3
Sub-Saharan	4	0.5
Others	2	0.2
Infants born in Spain	750	100
Parents born in Spain	714	94.9
Mothers born in Spain	702	93.6
<i>IWB^a</i>		
IWB <1500 g	9	1.2
IWB 1500–1999 g	27	3.6
IWB 2000–2499 g	76	10.2
IWB 2500–3499 g	453	61.2
IWB >3500 g	175	23.6
Exclusive breastfeeding <3 months	302	40.3
<i>Smoking</i>		
Smoking in pregnancy	99	13.2
Smoking in 1st trimester	83	11.0
Smoking in 2nd trimester	72	9.6
Smoking in 3rd trimester	66	8.8
Posterior smoking in mother	154	20.5
Posterior smoking in father	231	30.8
Eczema in the infant	92	12.2
<i>History of asthma</i>		
Mother	51	6.8
Father	29	3.8
Siblings	17	2.2
Humidity in the home	51	6.8
Air conditioning	75	10.0

^a IWB: infant weight at birth.

wheezing and RW in the first year of life. The odds ratios (ORs) and corresponding 95% confidence intervals (95%CI) were calculated.

Differences in the prevalence of wheezing or RW were observed in relation to infant weight at birth (IWB) – infants weighing under 1500 g and those weighing over 3500 g suffering more episodes of wheezing, but not RW – though not in relation to sex.

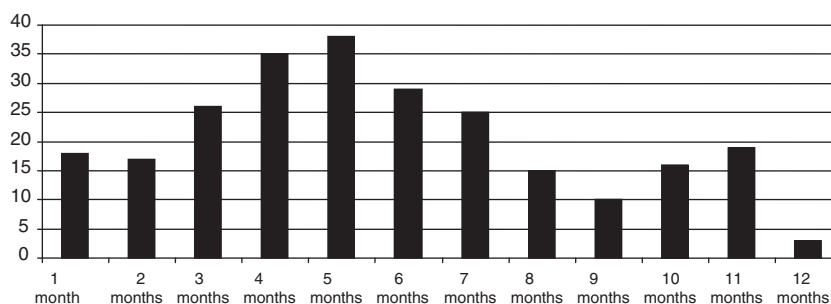


Figure 1 Patient age at the time of the first wheezing episode.

Table 2 Descriptive results for the children with wheezing.

Wheezing	<i>n</i>	%
<i>Infants with wheezing</i>		100
<i>Males with wheezing</i>	130	53.7
<i>Females with wheezing</i>	112	46.3
<i>Wheezing affects feeding</i>	112	46.3
<i>Wheezing limits parent activities</i>	95	39.3
<i>Wheezing affects family life</i>	61	25.2
<i>Waking up at night</i>		
Rarely (less than once a month)	87	35.9
Sometimes (some weeks in some months)	94	38.8
Often (two or more times a week, almost every month)	15	6.2
Never	46	19.1
Severe wheezing	82	33.8
Have visited the Emergency Department	112	46.2
Have been hospitalised due to wheezing	21	8.7
Have been diagnosed with asthma by the paediatrician	6	2.5
Wheezing tends to begin with normal cold	230	95
Wheezing starts or worsens on crawling, laughing or crying	75	31
<i>Treatment</i>		
Short-acting inhalatory β_2 -agonists	188	77.7
Inhalatory corticosteroids	64	26.4
Antileukotrienes	48	19.8
Ketotifen	15	6.2
Antileukotrienes + ketotifen	7	2.8

A total of 40.3% of the infants were exclusively breastfed (EBF) for ≤ 3 months, and 51.1% for longer periods of time – wheezing being observed in 36.1% of the former and in only 29.9% of the latter (OR 1.33, 95% confidence interval [0.98–1.81]). In addition, the infants breastfed for less than three months suffered RW in 14.5% of the cases, versus 10% of those with EBF for more than three months (OR 1.53 [0.98–2.38]).

A significant association was recorded between the infants experiencing their first cold in the first three months of life and the appearance of wheezing ($p=0.03$) (OR 1.43 [1.02–2.01]) and RW ($p=0.02$) (OR 1.67 [1.05–2.67]).

A total of 13.2% of the mothers were smokers during pregnancy, though overall smoking was not seen to exert a significant effect upon the presence of wheezing – except in the case of those mothers who smoked in the last three months of pregnancy: in this subgroup 42.4% of the infants suffered wheezing, versus 31.4% of those whose mothers did not smoke (OR 1.60 [0.96–2.68]). No association was recorded between smoking during pregnancy or after delivery and RW.

A total of 6.8% of the mothers had been diagnosed with asthma – no association being found between asthma, rhinitis or eczema in the mother, father or siblings and the presence of wheezing in the first year of life. However, a statistically significant correlation was observed between

maternal asthma and RW in the infant ($p=0.02$) (OR 2.19 [1.08–4.44]).

Wheezing was recorded in 53.2% of the infants who had experienced eczema, versus in 27.8% of those without skin disorders ($p=0.00$) (OR 2.72 [1.75–4.24]). Likewise, RW was documented in 22.8% of the children with eczema versus in 10.3% of those without ($p=0.00$) (OR 2.55 [1.48–4.42]).

A total of 27.9% of the infants attended nursery. Of these, 40.9% suffered wheezing, versus 29.3% of those who were not sent to the nursery ($p=0.00$) (OR 1.66 [1.19–2.31]). In addition, 16.3% of the infants attending the nursery experienced RW, versus 10.1% of those who did not – the differences between the two groups being statistically significant ($p=0.01$) (OR 1.71 [1.08–2.72]).

No association was found between wheezing and the presence of pets in the home at the time of birth, although the presence of hamsters ($p=0.03$) or cats ($p=0.03$) after birth was seen to exert a significant protective effect. In contrast, the presence of birds in the home after birth was significantly correlated to RW ($p=0.03$).

Lastly, no significant association was found between humidity or dampness in the home and wheezing: 35.2% and 8.5% of the infants living under humid conditions suffered wheezing and RW, respectively, versus 32.2% and 12.1% of those without humidity in the home.

Discussion

Wheezing is very common in the first months of life. A recent study of families with a low socioeconomic level in Latin America¹¹ has found that during the first year of life, 80.3% of all infants had suffered one or more wheezing episodes, 43.1% had recurrent wheezing (RW), and 13.3% had suffered pneumonia.

Although the magnitude of the problem is different in Europe, the ALSCAP study,¹² carried out in the city of Bristol (United Kingdom), found 21.5% of the infants under six months of age to have experienced wheezing at least once. In Spain there are few data available on the prevalence of wheezing in the first months of life, although in 2004 Garcia-Marcos published a study in which 80% of the 2347 Spanish paediatricians surveyed considered that the number of children with wheezing requiring treatment increased each year.¹³

The data obtained in the present study indicate that the prevalence of wheezing and RW in Salamanca – a province in central Spain located at a considerable distance from the coast – is 32.3% and 11.9%, respectively. Such data on wheezing and RW in the first year of life are similar to those published by a recent study¹⁴ referred to different Spanish cities such as Valencia (28.7% and 12.1%) or La Coruña (34.8% and 13.8%), but are clearly lower than those recorded in Cartagena (39.1% and 16.2%) or Bilbao (38.9% and 18.6%) – both of which are located on the coast. The prevalence of wheezing recorded in Salamanca is higher than that documented in Alzira, a city in the province of Valencia (Spain) at a certain distance from the coast (25.2% and 11.6%), yet the data relating to RW are similar.¹⁵ However, this study only contemplated infants in the first six months of life, and excluded preterm infants. We have found no data suggesting differences in the prevalence of wheezing and RW according

Table 3 Wheezing risk factors, odds ratio with 95% confidence interval.

	<i>n</i>	%	OR	95%CI OR
<i>Male</i>	130	53.7	1.06	0.78–1.44
<i>Exclusive breastfeeding ≤3 months</i>	109	44.9	1.33	0.98–1.81
<i>IWB</i>				
IWB 2500–3499 g			1	Reference
IWB <1500 g	7	4.9	8.18*	1.68–39.9
IWB 1500–1999 g	8	5.6	0.97	0.42–2.30
IWB 2000–2499 g	21	13.4	0.89	0.52–1.53
IWB >3500 g	68	33.3	1.49*	1.03–2.14
<i>Smoking</i>				
No smoking			1	Reference
Gestational	34	14.0	1.10	0.71–1.72
First trimester	27	11.1	1.00	0.62–1.63
Second trimester	25	10.2	1.12	0.67–1.87
Third trimester	28	11.6	1.60*	0.96–2.68
Mother after birth	51	21.1	1.03	0.71–1.50
Father after birth	81	33.4	1.19	0.86–1.66
<i>History of asthma</i>				
Father	6	2.4	0.53	0.21–1.32
Mother	21	8.6	1.50	0.84–2.68
Siblings	3	1.2	0.44	0.13–1.55
<i>History of rhinitis</i>				
Father	30	12.3	0.73	0.46–1.14
Mother	33	13.6	0.90	0.58–1.40
Siblings	4	1.7	0.75	0.24–2.38
Nursery attendance	85	35.3	1.66*	1.19–2.31
First cold ≤3 months	76	31.3	1.43*	1.02–2.01
Eczema in infant	49	20.3	2.72*	1.25–4.24
Pollution	15	6.1	0.66	0.36–1.21
Humidity in the home	18	7.4	1.14	0.63–2.08
Air conditioning	23	9.5	0.91	0.54–1.53
Carpet in the home	1	0.4	0.16	0.02–1.20
<i>Domestic pets</i>				
Cat after birth	3	1.2	0.29*	0.09–0.98
Hamster/rabbit after birth	6	2.5	4.24*	1.05–17.12
Birds after birth	14	5.7	1.08	0.56–2.11
<i>Maternal educational level</i>				
Elementary/incomplete secondary (≤11 years)			1	Reference
Complete secondary and higher (≥12 years)	99	75	0.95	0.59–1.55
University	111	77.1	0.84	0.52–1.35

IWB: infant weight at birth.

OR: odds ratio.

* $p < 0.05$.

to whether the location is on the coast or further inland, for individuals in this age range.

In the same way as in the already published international studies of the EISL,¹⁶ we found a first cold in the first three months of life to be a risk factor for wheezing and RW.

Forty-six percent of the children with wheezing (112 cases) visited the Emergency Department – these subjects representing 14.9% of the global sample – and of these, 2.8% (21 cases) required hospital admission. Such high figures may be a consequence of easy accessibility to healthcare in Salamanca, and differ from those recorded by

other Spanish studies¹⁵ in which 11.4% of the children with wheezing reported to the Emergency Department, with the admission of 4% of all wheezing infants.

Most wheezing episodes in small infants are due to viral infections,^{4,17} and such infections are probably the cause of the statistically significant results obtained in our study among infants attending the nursery, in coincidence with the observations of other authors studying this same age range.¹⁸

The present study has focused on factors other than infection which may be of relevance in relation to both

Table 4 Recurrent wheezing risk factors, odds ratio with 95% confidence interval.

	<i>n</i>	%	OR	95%CI OR
<i>Male</i>	52	58.4	1.31	0.83–2.05
<i>Exclusive breastfeeding ≤3 months</i>	44	49.4	1.53	0.98–2.38
<i>IWB</i>				
IWB 2500–3499 g			1	Reference
IWB <1500 g	1	1.7	0.87	0.11–7.09
IWB 1500–1999 g	1	1.7	0.27	0.04–2.01
IWB 2000–2499 g	7	10.9	0.70	0.31–1.59
IWB >3500 g	22	27.8	1.00	0.59–1.69
<i>Smoking</i>				
No smoking			1	Reference
Gestational	10	11.2	0.81	0.41–1.63
First trimester	10	11.2	1.02	0.51–2.06
Second trimester	10	11.2	1.22	0.60–2.48
Third trimester	10	11.2	1.37	0.67–2.79
Mother after birth	22	24.7	1.31	0.78–2.20
Father after birth	28	31.4	1.04	0.64–1.67
<i>History of asthma</i>				
Father	1	1.1	0.26	0.03–1.91
Mother	11	12.3	2.19*	1.08–4.44
Siblings	0	0.0	0.43	0.06–3.24
<i>History of rhinitis</i>				
Father	12	13.4	0.87	0.46–1.67
Mother	17	19.1	1.46	0.82–2.59
Siblings	3	3.3	1.87	0.52–6.77
Nursery attendance	34	38.2	1.72*	1.08–2.72
First cold ≤3 months	32	36	1.67*	1.05–2.67
Eczema in infant	21	33.9	2.55*	1.48–4.42
Pollution	5	5.6	0.64	0.25–1.65
Humidity in the home	4	4.4	0.61	0.22–1.75
Air conditioning	14	15.7	1.80	0.96–3.38
Carpet in the home	0	0.0	0.52	0.07–4.00
<i>Domestic pets</i>				
Hamster/rabbit at birth	4	4.4	4.40*	1.26–15.33
Cat after birth	0	0.0	0.30	0.04–2.23
Hamster/rabbit after birth	3	3.3	3.81*	0.94–15.50
Birds after birth	9	10.1	2.21*	1.02–4.80
<i>Maternal educational level</i>				
Elementary/incomplete secondary (≤11 years)			1	Reference
Complete secondary and higher (≥12 years)	39	78	1.17	0.57–2.38
University	39	78	0.92	0.45–1.88

IWB: infant weight at birth.

OR: odds ratio.

* $p < 0.05$.

wheezing and RW. In this context, and coinciding with other studies, we found no significant differences in terms of patient sex¹⁹ – in contrast to other authors who report a higher prevalence among males.^{11,15,16,20} On the other hand, we found an association between wheezing and infant weight at birth (IWB) of under 1500 g. The literature reports that infants with a low weight at birth are at an increased risk of suffering respiratory infections and wheezing,²¹ with implications later on in adult life.²² In coincidence with other investigators,²³ we likewise recorded more

wheezing in infants with IWB > 3500 g, although no such data have been obtained in other studies.^{15,24} We found no association between IWB and RW. Likewise, the statistically significant association we observed between both wheezing and RW and the presence of eczema in infancy coincides with the data published by other authors.^{3,16,20,25}

In agreement with other investigators,^{15,16,26} we found wheezing and RW to be significantly correlated to exclusive breastfeeding (EBF) for ≤3 months. In this context, it is still not clear whether the prolongation of EBF reduces the

frequency of wheezing, on the grounds that it is a protective factor against infections. A study has recently been published in which breastfeeding was found to imply a lesser risk of allergic sensitisation.²⁷ This contradicts other similar recent studies^{28,29} in which breastfeeding was found to protect against infections but could increase allergy and asthma at later ages.

The observed relationship between maternal asthma and RW coincides with the findings of other authors,^{16,19} and some studies regard maternal asthma to be a major risk factor for atopic wheezing in nursing infants.^{30,31}

Despite the extensive literature relating smoking in the mother during pregnancy and posterior exposure to tobacco smoke to the development of wheezing in children,^{5,32} we recorded no such association, except as refers to those mothers who smoke in the last three months of pregnancy, where a correlation was found to wheezing but not to RW. This was probably due to the relatively small number of smoking mothers involved, and to the lack of an objective method for the detection of the smoking habit.^{15,20}

In accordance with other investigators, the presence of pets in the home before or after birth was not seen to exert a significant influence.^{15,20} However, on individualising the type of pet, a statistically significant association was observed between the presence of cats or hamsters after birth and the appearance of wheezing and RW – although possibly a larger study series would be required in order to assess the clinical relevance of this finding.

University education on the part of the mother was not found to exert a significant influence,¹⁵ in contrast to the findings of studies made in Latin America.¹⁶

We observed no correlation between humidity or moisture in the home and wheezing or RW, in contrast to other European studies²⁰ where despite the limited number of cases involved (as in our own series), humidity was found to exert an influence. Likewise, such an association has also been reported by studies in Latin America, where there is a higher prevalence of humidity in the home.¹⁶

Although the 1998 International Pediatric Congress³³ established the concept of “nursing infant asthma”, only six parents of the 88 infants with three or more wheezing episodes recognised having received a diagnosis of asthma from the paediatrician. Probably, acceptance among the professionals in recent years of the concept of asthmatic phenotypes, and the concern generated among parents by a diagnosis of asthma, have caused physicians in most cases to inform parents that their child presents “recurrent wheezing”.

As possible limitations of our study, mention must be made of the fact that the data were produced by the parents in reply to the central wheezing questionnaire of the EISL, i.e., the data were not based on objective information supplied by the paediatricians. Nevertheless, the mentioned questionnaire has been correctly validated.⁸ Seasonal variability and the importance of viral infections in relation to the origin of wheezing may constitute a confounding factor, since viral ecology and virulence can have an impact, particularly in the winter months. However, this limitation has been minimised by including infants born in all seasons of the year. On the other hand, the main strengths of the study are its focus on the general population, with the participation of practically all the Primary Care paediatricians in the

province of Salamanca – both rural and urban, with different cultural and socioeconomic characteristics – the large size of the study sample, and the risk factors studied.

In summary, we have detected a high incidence of wheezing and recurrent wheezing in infants under one year of age, with a significant impact upon feeding, sleep, infant life in general, and family life. The main risk factors were nursery attendance, the presence of eczema in the infant, weight at birth, maternal asthma, exclusive breastfeeding for three months or less, a first cold in the first three months of life, and the presence of certain domestic pets.

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Conflict of interest

The authors have no conflict of interest to declare.

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