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ORIGINAL ARTICLE

Prevalence and risk factors associated with wheezing in the first year of life☆

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KEYWORDS
Prevalence;
Risk factors;
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Abstract
Objective: to investigate the prevalence and risk factors associated with wheezing in infants in the first year of life.
Methods: this was a cross-sectional study, in which a validated questionnaire (Estudio Internacional de Sibilancias en Lactantes - International Study of Wheezing in Infants - EISL) was applied to parents of infants aged between 12 and 15 months treated in 26 of 85 primary health care units in the period between 2006 and 2007. The dependent variable, wheezing, was defined using the following standards: occasional (up to two episodes of wheezing) and recurrent (three or more episodes of wheezing). The independent variables were shown using frequency distribution to compare the groups. Measures of association were based on odds ratio (OR) with a confidence interval of 95% (95% CI), using bivariate analysis, followed by multivariate analysis (adjusted OR [aOR]).
Results: a total of 1,029 (37.7%) infants had wheezing episodes in the first 12 months of life; of these, 16.2% had recurrent wheezing. Risk factors for wheezing were family history of asthma (OR = 2.12; 95% CI: 1.76-2.54) and six or more episodes of colds (OR = 2.38; 95% CI: 1.91-2.97) and pneumonia (OR = 3.02; 95% CI: 2.43-3.76). For recurrent wheezing, risk factors were: familial asthma (aOR = 1.73; 95% CI: 1.22–2.46); early onset wheezing (aOR = 1.83; 95% CI: 1.75-3.75); nocturnal symptoms (aOR = 2.56; 95% CI: 1.75-3.75), and more than six colds (aOR = 2.07; 95% CI 1.43- .00).

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Conclusion: the main risk factors associated with wheezing in Fortaleza were respiratory infections and family history of asthma. Knowing the risk factors for this disease should be a priority for public health, in order to develop control and treatment strategies.
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PALAVRAS-CHAVE
Prevalência;
Fatores de risco;
Estudos transversais;
Lactente

Prevalência e fatores de risco associados à sibilância no primeiro ano de vida

Resumo

Objetivo: verificar a prevalência e fatores de risco associados à sibilância em lactentes no primeiro ano de vida.
Métodos: estudo transversal, onde foi aplicado o questionário padronizado e validado (*Estudio Internacional de Sibilancias en Lactantes*-EISL) aos pais de lactentes com idade entre 12 e 15 meses que procuraram 26 das 85 unidades de atenção básica, no período 2006 a 2007. A variável dependente, sibilância, foi definida utilizando os seguintes padrões: ocasional (até dois episódios de sibilância) e recorrente (três ou mais episódios). As variáveis independentes foram apresentadas usando distribuição de frequências, utilizadas para comparar os grupos. As medidas de associações foram baseadas em razão de chances (*odds ratio*-OR), com intervalo de confiança de 95% (IC95%), com análise bivariada, seguida de análise multivariada (OR ajustada).
Resultados: um total de 1.029 (37,7%) lactentes apresentou sibilância nos primeiros 12 meses de vida e destes, 16,2% tiveram sibilância recorrente. Os principais fatores de risco associados à sibilância foram: história familiar de asma (ORa = 2,12; IC95%: 1,76-2,54); seis ou mais episódios de resfriado (ORa = 2,38; IC95%: 1,91-2,97) e pneumonia (ORa = 3,02; IC95%: 2,43-3,76) e sibilância recorrente foram: asma na família (ORa = 1,73; IC95%: 1,22-2,46); início precoce de sibilância (ORa = 1,83; IC95%: 1,75-3,75); sintomas noturnos (ORa = 2,56; IC95%: 1,75-3,75); mais de 6 resfriados (ORa = 2,07; IC95%: 1,43-3,00).
Conclusão: os principais fatores de risco associados à sibilância foram as infecções respiratórias e história de asma na família. Conhecer os fatores de risco dessa enfermidade deve ser uma prioridade para a saúde pública, que poderá desenvolver estratégias de controle e tratamento.
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Introduction

Wheezing is a very common symptom in infants,[1] which is usually accountable for a high demand of medical consultations and emergency care services, with relatively high rates of hospitalization. Along with acute respiratory infections, it plays an important role in infant mortality.[2] In Latin America, approximately 100,000 children die in the first year of life due to acute respiratory infection, and a significant proportion of them have a history of wheezing.[3] In Brazil, data from the Ministry of Health show that around 35% of infant hospitalizations in the first year of life in Brazil are due to respiratory diseases.[4]

Nevertheless, the real extent of this problem remains unknown, as well as how many of these infants are actually asthmatic patients.[5] The factors that establish the start, evolution, and prognosis of wheezing in infants have not yet been well defined. As it occurs in older children, it is likely that individual genetic and immunological patterns, associated with environmental factors, are responsible for most of wheezing phenotypes in childhood.[6,7] Most studies indicate a multifactorial etiology in the pathogenesis of wheezing in the first year of life, in addition to the close association with respiratory infections. However, how these different elements relate to each other is still the subject of much controversy.[8,9]

The International Study of Wheezing in Infants (Estudio Internacional de Sibilancias en Lactantes [EISL]) was developed in order to determine the prevalence and risk factors associated with wheezing in infants in the first year of life.[10] The EISL project evaluated the risk factors associated with wheezing in the first year of life in children from Latin America, Spain, and the Netherlands. Data showed a large variation in the prevalence and severity of wheezing at the centers, but with a tendency of higher prevalence and severity in Latin American children. The present study is part of the EISL project - phase 1.

This study aimed to determine the prevalence and risk factors associated with wheezing in infants in the first year of life, living in Fortaleza, Brazil, using the EISL protocol.

Methods

The present study was conducted in the city of Fortaleza, capital of the state of Ceará, Northeastern Brazil, as part of the EISL project - phase 1.[10] The EISL is a cross-sectional, multicenter, international study with descriptive and analytical elements, developed to assess the prevalence, severity, and other characteristics of wheezing in infants in the first year of life from Latin America, Spain, and the Netherlands. It was designed to determine the association of wheezing

with other respiratory diseases, especially pneumonia, and to define the risk factors for wheezing in infants in their first 12 months of life, similarly to the ''International Study of Asthma and Allergies in Childhood'' (ISAAC).[11]

The study was performed in 26 of 85 primary care units, selected at random and proportional to the demographic distribution in the six regions (regional executive secretariats [RES]) of Fortaleza. Each RES has its unique characteristics regarding geographic location (coastal region, peripheral region), distribution of income, territorial occupation, and extension.[12]

The study population comprised infants aged between 12 and 15 months, selected during routine consultations or immunizations. Children with chronic diseases in other systems who presented any respiratory impact (neuropathies, heart disease, severe somatic malformations and genetic diseases, among others) were excluded.

Data collection was conducted from December of 2006 to December of 2007 using the written questionnaire (WQ) of EISL as the collection tool, which was standardized and validated for the local environment (Brazilian culture) after being translated into Brazilian Portuguese.[13] The WQ-EISL comprises questions regarding demographic characteristics, wheezing, respiratory infections, and risk factors, namely: gender, age, ethnicity, birth weight and height, current weight and height, type of delivery, maternal schooling, characteristics of wheezing, medication use, hospitalization, association with pneumonia, and environmental and family factors, among others.

The questions are very sensitive, and are based on clinical practice as well as on international studies on infants, to ensure comparable information on the epidemiological and clinical issues related to this disease.

The dependent variable, wheezing, was defined in this study as the presence of wheezing or bronchitis in the first 12 months of the child's life, and categorized as occasional (up to two episodes of wheezing) or recurrent (three or more episodes of wheezing). The independent variables (exposure) were grouped according to demographic, socioeconomic, environmental, family, and clinical characteristics.

Data analysis

Data were organized in a standard format; data entry was performed using EPI INFO, version 3.5.1, and data analysis was conducted using STATA, version 10. The variables were shown using the distribution of frequencies and Pearson's chi-squared test was used to compare groups of infants. Measures of association were based on odds ratio (OR) with a 95% confidence interval (95% CI), with bivariate analysis followed by multivariate analysis (logistic regression-adjusted OR). In the univariate analysis, the association between each explanatory variable and the dependent variable (wheezing) was investigated separately, which was used as a selection criterion for the independent variables used in the final model. Then, these variables were included in the logistic regression model (adjusted OR), which evaluated the effect of the selected variables on the outcome. In this case, the influence of each explanatory variable was controlled by the effect of the others, eliminating potential confounders.

The study was approved by the Ethics Committees of the Universidade Federal do Ceará (No. 734/06 and COMEPE protocol 238/06) and of the Universidade Federal de São Paulo (No. 0804/09), in accordance with the Declaration of Helsinki. The research protocol was approved by the Health Secretariat of Fortaleza. Voluntary and anonymous participation was guaranteed by the informed consent given before the interviews.

Results

The study included 2,732 infants, of whom 1,024 (37.7%) had wheezing episodes in the first 12 months of life; 16.2% of these had recurrent wheezing, with three or more crises in the first year of life.

Around 57% of the wheezing infants were males, and 60% were of black or mixed-race ethnicity. The mothers of these infants had low educational level, 70% had no paid work, 18% were smokers, and 13% smoked during pregnancy. The wheezing infants had twice the incidence of family history of asthma when compared to non-wheezing infants, and three times greater history of colds and pneumonia. Table 1 shows the comparative analysis of wheezers and non-wheezers according to the demographic, socioeconomic, environmental, family, and clinical characteristics of the study population.

Recurrent wheezers had more severe symptoms, nocturnal symptoms, and visits to emergency rooms and hospitalizations for wheezing and pneumonia, when compared to infants with occasional wheezing. Around 60% of recurrent wheezers had the first crisis of wheezing before 4 months of age, 41.9% had over six episodes of colds in the first year of life, 36.3% had pneumonia in the first year of life, and 50.9% had a family history of asthma (Table 2).

The comparative analysis between the groups identified several isolated factors that were then evaluated separately regarding the outcome (wheezing). The univariate analysis identified possible risk and protective factors. Then, the independent variables were selected to constitute the logistic regression model (adjusted OR), in order to control and eliminate possible confounding variables.

There was an association of wheezing with male gender, low maternal education, family history of asthma and dermatitis, mold in the household, and maternal smoking during and after pregnancy. There was also a significant association of wheezing with dermatitis and high number (six or more) of cold and pneumonia episodes in the first year of life. Maternal breastfeeding lasting less than four months was also a risk factor, as shown in Fig. 1.

The main risk factors associated with recurrent wheezing were familial asthma, early onset of wheezing, nocturnal symptoms, over six episodes of colds, asthma diagnosis, and severe symptoms (Fig. 2).

Discussion

Many studies worldwide have observed a high prevalence of wheezing during the first years of life. The first international comparison of EISL[14] studied over 30,000 children from 17 centers in Europe and Latin America, including eight in Brazil. The recently published data demonstrated that

Table 1 Comparative analysis between wheezers and non-wheezers in the first year of life, according to the demographic, socioeconomic, family, and clinical characteristics.

Variables	Wheezer 1,024 (37.66%) n (%)	Non-wheezers 1,703 (62.34%) n (%)	p[a]
Gender			
Male	586 (57.2)	889 (52.2)	
Female	439 (42.7)	814 (47.8)	0.009
Birth weight (kg)	3.259 kg (SD = 0.6)	3.256 kg (SD = 0.6)	-
Current weight (kg)	10.5 kg (SD = 0.1)	10.3 kg (SD = 1.4)	-
Birth height	49.4 cm (SD = 2.6)	49.4 (SD = 2.4)	-
Current height	75.2 (SD = 3.4)	75.8 (SD = 3.5)	-
Start of wheezing (months)	4.7 (SD = 3)	-	-
Ethnicity			0.831
White	423 (41.1)	693 (40.7)	
Black	601 (58.4)	1006 (59.1)	
Asian	5 (0.5)	4 (0.2)	
Maternal schooling			0.073
Elementary school	463 (45.0)	762 (44.7)	
Incomplete high school	346 (33.6)	526 (44.7)	
Complete high school and college/university	220 (21.4)	415 (24.4)	
Three or more siblings	66 (6.4)	111 (6.5)	0.915
Five or more persons in the household	516 (50.15)	831 (48.8)	0.494
Paid work (mother)	247 (24.0)	468 (27.5)	0.045
Attends daycare	37 (3.6)	61 (3.6)	0.985
Mold in the household	330 (32.1)	497 (29.2)	0.112
Air pollution	751 (73.0)	1,229 (72.1)	0.643
Smokers in the household	540 (52.7)	751 (52.8)	< 0.0001
Mother is a smoker	187 (18.2)	221 (13.0)	< 0.0001
Mother smoked during pregnancy	134 (13.0)	120 (7.0)	< 0.0001
Pet in the household (currently)	679 (74.2)	1,263 (65.0)	< 0.0001
Kitchen in the household	1204 (70.7)	805 (78.2)	< 0.0001
Cell phone in the household	455 (44.2)	541 (31.8)	< 0.0001
Updated vaccination schedule	1024 (100)	1,625 (95.4)	0.312
C-section delivery	432 (42.2)	730 (42.9)	0.724
Early weaning (Breastfeeding for less than four months)	450 (43.7)	1,087 (63.8)	< 0.0001
Family history of asthma	431 (41.9)	366 (21.5)	< 0.0001
Family history of rhinitis	436 (42.6)	571 (33.5)	< 0.0001
Family history of dermatitis	186 (18.2)	179 (10.5)	< 0.0001
Atopic dermatitis	604 (59.0)	811 (47.6)	< 0.0001
Six or more colds	282 (27.4)	184 (10.8)	< 0.0001
Age at start of colds < 4 months	456 (44.5)	611 (35.9)	< 0.0001
Pneumonia	310 (30.3)	180 (10.6)	< 0.0001
Hospitalization due to pneumonia	171 (16.7)	84 (4.9)	< 0.0001

SD, standard deviation.
[a] p-value (Pearson's chi-squared test).

there is a great variability in the prevalence and severity of wheezing in the different centers, but with a tendency to higher prevalence and severity in children from Latin America.

The prevalence of wheezing in that study, considering the total study population, was 45.2%, 20.3% of which corresponded to recurrent wheezing. When the data was stratified for Latin America, the prevalence was 47.3% and 21.4% for wheezing and recurrent wheezing, respectively, and for Europe, 34.4%, and 15.0%, respectively.[14] In Brazil, the prevalence of wheezing in the first year of life ranged between 43% and 63.6%, and 21.9% and 36.6% for occasional and recurrent wheezing, respectively. The values observed here show great variability; this difference is possibly associated with differences in climatological, environmental, and socioeconomic characteristics of different regions.[14]

This study observed a prevalence of 37.7% for occasional wheezing and 16.2% for recurrent wheezing; this prevalence

Table 2 Comparison between infants that are occasional and recurrent wheezers, according to the clinical features and family history.

Variables	Occasional wheezer < three crises n = 580 (%)	Recurrent wheezer ≥ three crises n = 444 (%)	p[a]
Male gender	309 (53.3)	277 (37.6)	0.003
Pneumonia	149 (25.7)	161 (36.3)	< 0.0001
Hospitalization due to pneumonia	79 (13.6)	92 (20.7)	0.003
Hospitalization due to bronchitis	29 (5)	165 (37.6)	<0.0001
Passive smoking	307 (52.9)	233 (52.5)	0.885
Maternal smoking	92 (15.9)	95 (21.4)	0.024
Mother smoked during pregnancy	68 (11.7)	66 (14.9)	0.140
History of asthma in the family	205 (35.3)	226 (50.9)	< 0.0001
History of rhinitis in the family	255 (43.9)	181 (40.8)	0.305
History of dermatitis in the family	98 (16.9)	88 (19.8)	0.229
Dermatitis	331 (57.1)	273 (61.5)	0.154
Six or more colds	96 (16.5)	186 (41.9)	< 0.0001
Age at start of colds < 4 months	204 (35.2)	252 (56.8)	< 0.0001
Age of wheezing < 4 months	182 (37.7)	238 (60.7)	< 0.0001
Updated vaccination schedule	580 (100)	444 (100)	0.451
C-section delivery	244 (42.1)	188 (42.3)	0.930
Use of bronchodilator	461 (82.6)	371 (85.3)	0.257
Use of inhaled corticoids	120 (23.7)	89 (22.9)	0.786
Use of antileukotrienes	23 (4.9)	10 (2.9)	0.152
Visits to the emergency room	360 (62.1)	346 (77.9)	< 0.0001
Severe episodes	374 (47.2)	278 (62.6)	< 0.0001
Hospitalization due to wheezing	75 (12.9)	117 (26.3)	< 0.0001
Diagnosis of asthma	59 (10.2)	91 (20.5)	< 0.0001
Frequent nocturnal symptoms	930 (16.0)	185 (41.7)	< 0.0001
Maternal breastfeeding < 4 months	163 (31.5)	145 (35.8)	0.634

[a] p-value (Pearson's chi-squared test).

of recurrent wheezing is below that found in other studies using the EISL protocol,[10] especially in Brazil.

The identification of the determinants of wheezing in infants has been the subject of several studies. In fact, several factors appear to play a decisive role in the triggering and maintenance of wheezing in infants, such as genetic, immunological, and environmental variables, as well as infection and maternal breastfeeding, among others.

This study showed a significant association of wheezing with respiratory infection for all types of wheezing. Respiratory infections are common in childhood and have an important role in infant morbimortality. They require several outpatient clinic visits, hospital admissions, and consequently increase public health care costs in many countries.[15] There appears to be an important association between respiratory infections, particularly those caused by viruses, and the pathogenesis of wheezing in childhood.[16,17]

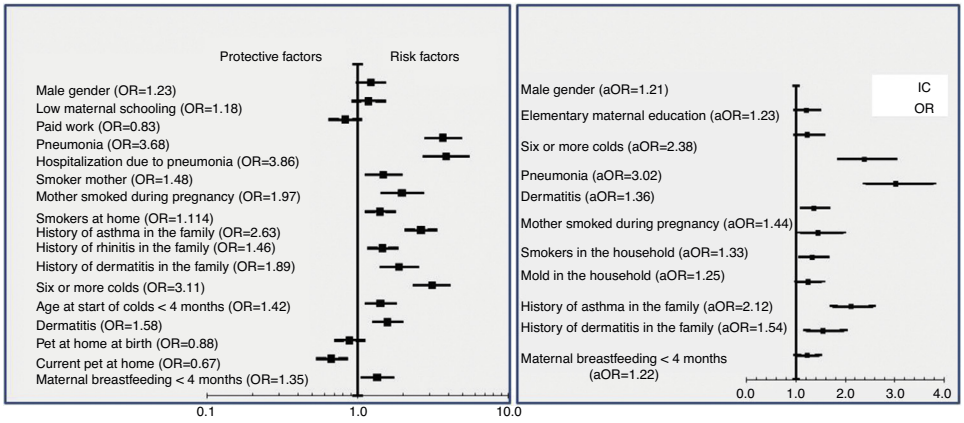

Figure 1 Factors associated with wheezing in the first year of life. aOR, adjusted odds ratio.

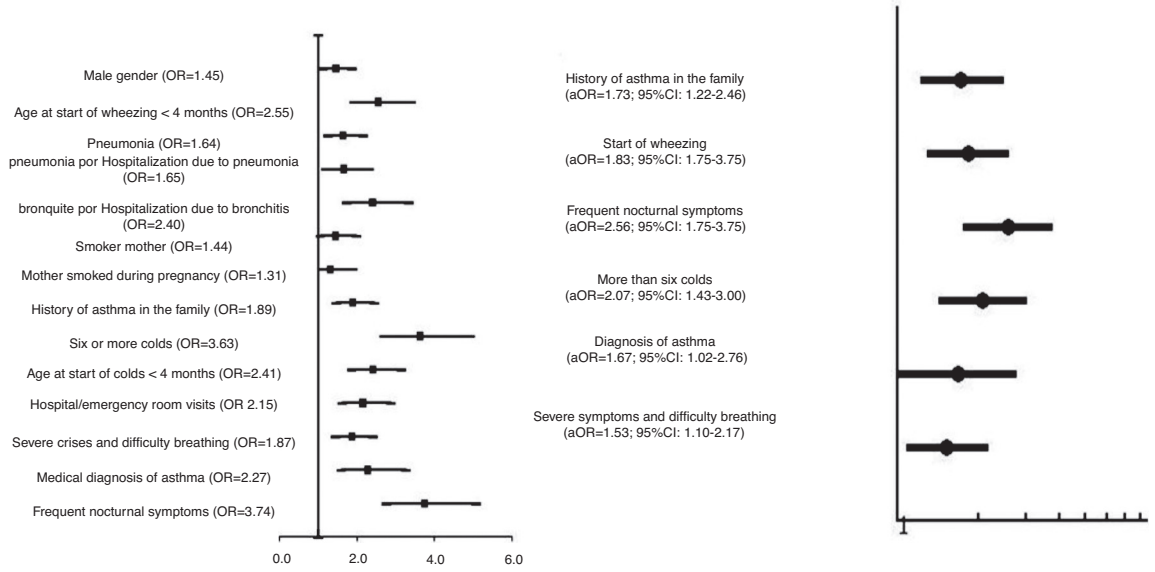

Figure 2 Risk factors associated with recurrent wheezing in infants in the first year of life. CI, confidence interval; aOR, adjusted odds ratio.

The EISL showed a significant association between the occurrence of colds in the first three months of life and wheezing in infants in countries from Europe and Latin America, especially those with recurrent wheezing.[18]

Other factors also contribute to the risk of wheezing. In this study, a correlation was observed between wheezing and low maternal education, male gender, family history of asthma, and dermatitis. Several studies indicate genetics as a determinant factor for allergic diseases.[19,20] The EISL demonstrated a statistically significant association between wheezing and factors such as family history of asthma and rhinitis.[18] It also showed the association of wheezing with the male gender, especially in European countries when compared to Latin America.[18] The male gender has been identified as a risk factor for wheezing during the first years of life in several studies.[21]

Other factors also contribute to the risk of wheezing in infants. In this study, early weaning, defined as maternal breastfeeding lasting less than four months, appeared as a risk factor. Breastfeeding is widely promoted as an important factor in reducing the risk for atopy and asthma; however, the evidence for this effect is still very conflicted.[22]

A prospective study performed in New Zealand with approximately 1,000 children indicated that breastfeeding is not a protective factor and may even increase the risk for atopy.[23] Other studies, in contrast, have demonstrated that exclusive breastfeeding has a significant protective effect against the development of recurrent wheezing, asthma, and atopy. However, this protective effect appears to be mediated by nutrients and individual protection mechanisms and, to a lesser extent, to factors related to atopy.[24]

This study demonstrated an association between wheezing and maternal smoking during and after pregnancy. The harmful effects of smoking on children's health are well known, but their potential impact on early lung development is less clear.[25] It is difficult to separate the effects of pre- and postnatal exposure, as most women who continue to smoke during pregnancy (approximately 30% worldwide) do not stop the habit after the child is born[26]

However, assessments conducted before any postnatal exposure have shown significant changes in lung function in newborns whose mothers smoked during pregnancy, and the persistence of tobacco exposure in the postnatal period probably increases the risk of respiratory diseases.[27] A study conducted in Spain with over 20,000 children and adolescents demonstrated that environmental tobacco smoke is associated with a higher prevalence of asthma symptoms, particularly if the mother or both parents smoke.[28]

In the present study, infants with recurrent wheezing episodes had early-onset wheezing, severe episodes, difficulty breathing, nocturnal symptoms, family history of asthma, and a medical diagnosis of asthma. The EISL found similar results, especially in Latin American countries[18] and in Brazilian cities.[29]

Some potential limitations of this study were identified, such as the very homogeneous study population (mostly low-income) and its cross-sectional design, which could possibly influence the results. In addition, interviews with parents or caregivers about events that occurred during the infants' first year of life may depend on the ability of respondents to recall facts, especially regarding questions that contain a high degree of subjectivity, such as the those related to family history.

Another important possible limitation was the evaluation of outcomes (wheezing) in this study, which was based on information collected during interviews rather than on medical records. However, the fact that the present study is multicenter and that all the data come from different national and international centers may minimize these limitations.

In summary, this study demonstrated a prevalence of recurrent wheezing in the city of Fortaleza that is below

those found in other studies using the EISL protocol, especially in Brazil. It also evidenced a strong association of wheezing with a history of respiratory infections, asthma, and atopic dermatitis in the family. Moreover, it demonstrated that infants with over three episodes of wheezing had difficulty breathing, severe episodes, nocturnal symptoms, and a medical diagnosis of asthma.

This study indicates a multifactorial pathogenesis of wheezing in the first year of life, which is closely related to respiratory infections.Considering that many cases of asthma present the initial symptoms early in the first year of life, it should be a priority of public health policy to know the prevalence and risk factors of this disease, in order to develop control and treatment strategies that impact on morbidity and mortality of these diseases, and improve the quality of life of these children and their families.

Conflicts of interest

The authors declare no conflicts of interest.

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