

## Occurrence of infectious diseases during the first two years and symptoms of asthma in six-year-old children

Ocorrência de doenças infecciosas nos dois primeiros anos e sintomas de asma em crianças de seis anos de idade

Aparición de enfermedades infecciosas durante los dos primeros años y síntomas de asma en niños de seis años

Received: 01/20/2022 | Reviewed: 01/28/2022 | Accept: 01/31/2022 | Published: 02/01/2022

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### Abstract

**Objective:** To observe possible association between the occurrence of infectious diseases during the first two years of life and the occurrence of asthma symptoms in six-year-old children. **Methods:** Cross-sectional study involving 956 six-year-old schoolchildren. Asthma symptoms were assessed through International Study of Asthma and Allergies in Childhood questionnaires. Socio-demographic data, mother-reported infectious diseases during the child's first two years of life, family history of asthma and breastfeeding were included. Multivariate analysis was performed with all significant variables and those with a p-value <0.20 using Poisson Regression with a robust estimator. **Results:** The reported wheezing or whistling in the chest in the past 12 months prevalence was 18.7%. There was found a 9% higher prevalence of asthma at six years of age in children who had had respiratory infections in the first two years of life. Children with a family history of asthma had a 7% higher and independent prevalence of asthma at six years of age and those breastfed presented 6% lower independent prevalence of asthma at six years of age. **Conclusions:** Higher prevalence of asthma reports at six years of age was found in children whose mothers reported infectious respiratory diseases during the first two years and with family history of asthma. Lower prevalence was observed in breastfed children in the first two years of life.

**Keywords:** Asthma; Infectious diseases; Breast-feeding; Children.

### Resumo

**Objetivo:** Observar possível associação entre a ocorrência de doenças infecciosas nos dois primeiros anos de vida e a ocorrência de sintomas de asma em crianças de seis anos. **Métodos:** Estudo transversal envolvendo 956 escolares de seis anos. Os sintomas de asma foram avaliados por meio de questionários do *International Study of Asthma and Allergies in Childhood*. Foram incluídos dados sociodemográficos, doenças infecciosas relatadas pela mãe nos dois primeiros anos de vida da criança, história familiar de asma e amamentação. A análise multivariada foi realizada com todas as variáveis significativas e aquelas com valor de  $p < 0,20$  usando Regressão de Poisson com um estimador robusto. **Resultados:** A prevalência relatada de sibilos no peito nos últimos 12 meses foi de 18,7%. Encontrou-se prevalência 9% maior de asma aos seis anos de idade em crianças que tiveram infecções respiratórias nos dois primeiros anos de vida. Crianças com história familiar de asma apresentaram prevalência independente de asma 7% maior aos seis anos de idade e aquelas amamentadas apresentaram prevalência independente de asma 6% menor aos seis anos de idade. **Conclusões:** Maior prevalência de relato de asma aos seis anos de idade foi encontrada em crianças

cujas mães relataram doenças respiratórias infecciosas nos primeiros dois anos e com história familiar de asma. Menor prevalência foi observada em crianças amamentadas nos primeiros dois anos de vida.

**Palavras-chave:** Asma; Doenças infecciosas; Amamentação; Crianças.

### Resumen

Objetivo: Estudiar una posible asociación entre la aparición de enfermedades infecciosas en los dos primeros años de vida y los síntomas del asma en niños de seis años. Métodos: Estudio transversal en 956 escolares de seis años. Los síntomas del asma se midieron mediante el cuestionario del *International Study of Asthma and Allergies in Childhood*. Se incluyeron datos sociodemográficos, reportes de madres de enfermedades infecciosas en los dos primeros años de vida del niño, antecedentes familiares de asma y lactancia materna. Se realizó un análisis multivariado con todas las variables significativas y aquellas con un valor de  $p < 0,20$  mediante Regresión de Poisson con un estimador robusto. Resultados: La prevalencia de notificar la aparición de sibilancias en los últimos 12 meses fue del 18,7%. Se encontró una prevalencia 9% mayor e independiente de asma a los seis años de edad en niños que tenían infecciones respiratorias en los primeros dos años de vida. Los niños con antecedentes familiares de asma tenían una prevalencia de asma un 7% más alta e independiente a los seis años de edad, y los que fueron amamantados tenían una prevalencia de asma un 6% más baja e independiente a los seis años de edad. Conclusiones: Se encontró una mayor prevalencia de asma reportada a los seis años de edad en niños cuyas madres reportaron enfermedades respiratorias infecciosas en los primeros dos años y con antecedentes familiares de asma. Se observaron prevalencias más bajas en niños que fueron amamantados en los dos primeros años de vida.

**Palabras clave:** Asma; Enfermedades infecciosas; Amamantamiento; Niños.

## 1. Introduction

Asthma is a complex, multifactorial disease resulting from the interaction between genetic and environmental factors (Asher et al., 1995). Its pathophysiology is not fully understood. Environmental exposures and specific infections act on a predisposed genome that can lead to changes in the responses of the immune system, a factor that is associated to the appearance of asthma (Asher et al., 1995). Asthma, according to the Global Initiative for Asthma (GINA), is defined as a chronic inflammatory disease of the airways and manifests itself through respiratory signs and symptoms such as dyspnea, wheezing, chest tightness or chest discomfort and cough (Global Initiative for Asthma, 2022). Such findings vary in intensity over time and are usually accompanied by variable limitation of the expiratory flow (Global Initiative for Asthma, 2022).

Studies show that the period between conception and the first two years of life has a great influence on the risk of future development of allergic diseases (Wopereis et al., 2014; Wegienka et al., 2015). Because this time interval is decisive in the child's health, clinical situations that occur in this period may generate a higher risk of asthma development, when compared to later stages of childhood (Holt et al., 2005). In addition, episodes of respiratory disorders in the first years of life have a greater influence on the late onset of asthma in relation to a particular viral trigger (Bonnelykke et al., 2015).

Several aspects related to the first years of life are strongly associated to the prevalence of asthma, such as prematurity (Bacharier, 2014), breastfeeding (Friedman et al., 2005; Lodge et al., 2015), low birth weight (Xu et al., 2010; Xu et al., 2014), smoking mother (Tanaka et al., 2008), use of antibiotics by the child (Tanaka et al., 2008; Penders et al., 2011), neonatal jaundice (Das et al., 2015), exposure to mold and moisture (Tischer et al., 2011) and occurrence of specific respiratory infections (Bonnelykke et al., 2015).

Based on this multifactorial prevalence of asthma, epidemiological studies use tools that can identify individuals with asthma symptoms. In order to standardize and apply more easily and in a more reliable manner to these studies, the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires were applied. They are designed to identify children with symptoms and the severity of the disease based on cardinal symptoms (Sociedade Brasileira de Pneumologia e Tisiologia, 2012). These are standardized questionnaires that were developed and had their applicability, validity and reproducibility tested. Because of their advantages in terms of costs, convenience, and because they have relatively high sensitivity and specificity, ISAAC questionnaires have been widely used to investigate the prevalence and severity of asthma and other allergic diseases in population-based studies (Lai et al., 2009; Mallol et al., 2013). Results from phase III of the

ISAAC study, conducted in the 1990s, which included 98 countries, showed that the global prevalence of asthma was 11.7% in the 6 to 7 years of age group (Mallol et al, 2013). Brazil is among the countries with the highest prevalence of asthma in the world and it is believed that the rate is still growing in this age group (Mallol et al, 2013).

Therefore, knowledge about the risk and protection factors present in the first two years of life can assist in approaches and interventions capable of modifying the prevalence of asthma in childhood. Therefore, the association of infectious diseases, children's susceptibility and the response to infections in general is of great interest for the development of public health policies. It is also relevant for the development of new clinical treatments for asthma. Based on the above, the present study aimed to assess the potential association between the occurrence of infectious diseases in the first two years of life and the occurrence of asthma symptoms in children at six years of age.

## 2. Methodology

This is an epidemiological study with a cross-sectional design using data from the study named *Coorte Brasil Sul* (Traebert et al., 2018). The study population consisted of six-year-schoolchildren residents of Palhoça/SC, southern Brazil and enrolled in 37 public schools and 17 private schools, for a total of 1,756 children. The sample size was calculated based on the following parameters: population size: 1,756 children, 95% confidence level, anticipated prevalence of asthma symptoms unknown (P= 50%), relative error 3%. Thus, the minimum sample number was 665. As the total number of children with information needed for the present study was 956, it was decided that the sample would be composed of all children with the necessary information available in the database. The inclusion criterion was the presence of ISAAC data in the database of the *Coorte Brasil Sul*.

The *Coorte Brasil Sul* study collected data through interviews with mothers in households. In their absence, data were collected with the child's primary caregiver. The investigation team was responsible for collecting the data, using staff duly trained to collect them.

The dependent variable was the report of asthma symptoms at six years of age through the ISAAC question "Has your child had wheezing or whistling in the chest in the past 12 months?" (yes or no). The sociodemographic variables were gender of the child (male or female) and child's ethnicity (categorized as Caucasian or non-Caucasian). Independent variables were smoking during pregnancy (yes or no); family history of asthma (yes or no); breastfeeding (yes or no) and report of infectious diseases in the first two years of life: diarrhea (yes or no); chickenpox (yes or no); rubella (yes or no); respiratory infections (yes or no); otological infections (yes or no); tonsillitis (yes or no).

The data were analyzed using the SPSS 18.0 software. Bivariate and multivariate analyses were performed using Poisson Regression with a robust estimator. The multivariate model consisted of all significant variables and those with a p-value <0.20 in the bivariate. The prevalence ratios and their confidence intervals were estimated. Statistically significant and independent variables were those with a p-value <0.05.

This study complied with the ethical principles established by the Resolution of the Brazilian National Health Council No. 466/2012. Parents or guardians who agreed that their child participate in the investigation signed a Free and Informed Consent Form. The research project was submitted to and approved by the Research Ethics Committee of the *Universidade do Sul de Santa Catarina*, Brazil, under CAAE No. 38240114.0.00005369.

## 3. Results

A total of 956 schoolchildren were included in the study, of which 491 (51.4%) were male and 465 (48.6%) female. About 83% were Caucasian. As for the family history of asthma, 45.7% reported occurrence of siblings in the mother, father, or other family members. 13.5% of women smoked during pregnancy.

In relation to the report of infectious diseases in the first two years of the children's life, diarrhea occurred in 54.9% of the individuals, chickenpox in 25.2%, respiratory infections in 21.1% (Table 1).

**Table 1** – Report of infectious diseases and breastfeeding in the first two years of life in six-year-old-schoolchildren.

VARIABLES	n	%
<b>VARICELA (n= 930)</b>		
Yes	234	25.2
No	696	74.8
<b>RUBELLA (n= 947)</b>		
Yes	9	1.0
No	938	99.0
<b>RESPIRATORY INFECTIONS (n= 948)</b>		
Yes	200	21.1
No	748	78.9
<b>TONSILLITIS (n= 942)</b>		
Yes	484	51.4
No	458	48.6
<b>OTOLOGICAL INFECTIONS (n= 935)</b>		
Yes	336	35.9
No	599	54.1
<b>DIARRHEA (n= 921)</b>		
Yes	505	54.9
No	416	45.1
<b>BREASTFEEDING (n= 953)</b>		
Yes	872	91.5
No	81	8.5

Source: Authors.

According to the ISAAC questionnaire, the reported occurrence of wheezing or whistling in the chest in the past 12 months was 18.7% (95% CI 16.2; 21.1). The results of the bivariate and multivariate analysis are shown in Table 4. There was a 9% higher and independent prevalence of asthma at six years of age in children who had had respiratory infections in the first two years of life [PR= 1.09 (95% CI 1.04; 1.13)  $p < 0.001$ ]. On the other hand, children with a family history of asthma had a 7% higher and independent prevalence of asthma at six years of age [PR= 1.07 (95% CI 1.03; 1.10)  $p < 0.001$ ] and those breastfed in the first two years of life, presented 6% lower independent prevalence of asthma at six years of age [PR= 0.94 (95% CI 0.88; 0.99)  $p = 0.049$ ].

**Table 2** – Results of the association study.

VARIABLES	PR <sub>c</sub>	95% CI	p	PR <sub>a</sub>	95% CI	p
<b>GENDER</b>			0.066			0.338
Male	1.00			1.00		
Female	1.03	0.99-1.05		1.01	0.98-1.04	
<b>RESPIRATORY INFECTIONS</b>			<0.001			<0.001
Yes	1.11	1.07-1.16		1.09	1.04-1.13	
No	1.00			1.00		
<b>TONSILLITIS</b>			<0.001			0.066
Yes	1.07	1.04-1.10		1.03	0.99-1.06	
No	1.00			1.00		
<b>OTOLOGICAL INFECTIONS</b>			<0.001			0.244
Yes	1.06	1.02-1.09		1.02	0.99-1.06	
No	1.00			1.00		
<b>DIARRHEA</b>			<0.001			0.965
Yes	1.06	1.03-1.09		1.01	0.97-1.03	
No	1.00			1.00		
<b>SMOKING DURING PREGNANCY</b>			0.007			0.084
Yes	1.04	1.01-1.09		1.01	0.96-1.05	
No	1.00			1.00		
<b>FAMILY HISTORY OF ASTHMA</b>			<0.001			<0.001
Yes	1.10	1.07-1.13		1.07	1.03-1.10	
No	1.00			1.00		
<b>BREASTFEEDING</b>			<0.001			0.049
Yes	0.90	0.85-0.96		0.94	0.88-0.99	
No	1.00				1.00	

PR<sub>c</sub> = Crude Prevalence Ratio. PR<sub>a</sub> = Adjusted Prevalence Ratio. 95% CI = 95% Confidence Interval. Omnibus test p= 0.541. Source: Authors.

#### 4. Discussion

In the present study, the prevalence of asthma symptoms reports was found to be 18,7% in schoolchildren aged 6 years, using ISAAC's "wheezing or whistling in the chest in the past 12 months". Comparing with studies with a similar sample and instrument, a prevalence of 31.2% was observed in the State of São Paulo, when the variable "affirmative answer to the question about wheezing in the last year" was used (Casagrande et al., 2008), while a study from Amazonas State showed 25.2% asthma prevalence among schoolchildren. The following symptoms were more prevalent: wheezing sometime in life, wheezing in the last 12 months, from one to three wheezing attacks during the year and dry cough (Rosa et al, 2009).

Asthma is a complex and multifactorial disease, usually characterized by chronic inflammation of the airways, with a history and respiratory symptoms that have genetic-environmental factors that are determinants of an allergic phenotype (Asher et al., 1995; Global Initiative for Asthma, 2022). Considering this multifactoriality, aspects related to the first years of life are strongly connected with the prevalence of asthma, such as prematurity (Bacharier, 2014), low birth weight (Xu et al., 2010; Xu et al., 2014), neonatal jaundice (Das et al., 2015), exposure to mold and humidity (Tischer et al., 2011) and smoking mother (Tanaka et al., 2008).

Thus, the current study allowed observing an association between the presence of infectious diseases at an earlier age and the subsequent manifestation of asthma symptoms at six years of age. Thus, respiratory infections were shown to be statistically significant and independently associated with the reporting of asthma symptoms at six years of age. The

pathophysiological correlation between these variables is indicated in studies that explain that the genes encoding molecules involved in the innate immune response and inflammation are strong predictors and contribute to the development of asthma (Friedman et al., 2005). The number of episodes of respiratory disorders symptoms in the first years of life, a stage in which the respiratory and immune systems are still developing (Wegienka et al., 2015), has a greater influence on the late onset of asthma in relation to the occurrence of specific respiratory infections caused by the main viruses, such as the respiratory syncytial virus, rhinovirus, parainfluenza virus (Friedman et al., 2005; Rathinam et al., 2016; Lopes et al., 2022) and impairments of the coding of the interleukin pathway (Bonnelykke et al., 2015). Situations of this nature interfere with the immune system activation, such as inducing the typical inflammation of allergic asthma by differentiation. These inflammatory responses are critical for resolving infections and repairing tissue damage. Such activations form complexes that are involved in chronic inflammation and that represent the main contributor to different multifactorial diseases, in addition to contributions that are related to infections present in early life (Rathinam et al., 2016). Scientific evidence supports that the occurrence of these infections is one of the main antecedents of asthma in childhood, altering both epithelial cell homeostasis, pulmonary function and airway remodeling (Beigelman et al., 2016; Leal et al., 2018). Understanding the potentially modifiable factors and the associations between impairments of the respiratory system, together with changes in the formation of the immune system and the development of asthma is essential. Bonnelykke et al. (2015) suggest that the number of episodes of respiratory tract infections causing immune responses is associated with the development of asthma in schoolchildren, as opposed to a specific viral trigger.

In addition, studies (Tanaka, et al., 2008; Penders et al., 2011) have demonstrated that the use of antibiotics necessary to treat infectious diseases in children brings changes in the development of the immune system during childhood, considering the possibility that they cause changes in the gastrointestinal microbiology and/or in the airways microbiota. Other studies (Bonnelykke et al., 2015; Perez-Losada et al., 2015; Leal, et al., 2018) show that the metabolism of bacterial communities and epithelial cells in the nasal cavity differ between asthmatic and non-asthmatic children, which may impact the individual's metabolic regulation during inflammatory responses. These and other conditions that in interaction with the body during the period from conception to the first two years of life exert a great influence on the child's health, and are related to the predisposition of several diseases, lead also to an increased risk of asthma development (Holt et al., 2005).

In addition, the period from conception to the first two years of life is an important risk determinant for the development of diseases, including allergic diseases and children general health conditions (Wopereis et al., 2015; Wegienka et al., 2015). Certain exposures during this period can lead to reprogramming in response to temporary changes and the possible appearance of allergies, as well as metabolic changes, cardiovascular diseases, obesity and behavioral and neurological problems (Wopereis et al., 2015). Although the relationship between the first two years of life and immunological diseases is not yet well understood, it is believed that this period is fundamental for the appearance of asthma because in these first years of life, the infant's immune and respiratory systems are still developing. Thus, situations that occurred during an earlier time appear to have a greater impact on the risk of asthma development when compared to conditions seen in later stages (Wopereis et al., 2015; Wegienka et al., 2015).

On the other hand, family genetics has a direct relationship with the presence of asthma, with its occurrence in parents being an important predictor of occurrence in offsprings (Chatkin et al., 2005), a condition which was observed in the present study. A study by Perez-Losada et al. (2015) highlights that the chance of a child developing asthma is three times greater in families with at least one asthmatic parent, and six times greater when both parents are asthmatic, thus reaffirming the role of the active genetic effects in asthma due to the strong associations between certain genetic variants of this disease (Ullemar et al., 2016). The present study corroborates this fact, since it was observed that individuals with asthmatic parents have a 12% higher symptoms prevalence for such disease.

Breastfeeding in the present study stood out as being a protective factor for asthma. Breast milk protection can be explained by the presence of different immunological compounds, creating a passive immunization condition through bioactive components such as IgA and IgG, which are basic child defense mechanisms, and also through the supply of immunomodulators, anti-inflammatories, nutrients and other compounds that are not present in non-breast milk. In addition, non-breast milk may contain potentially allergenic components (Silva et al., 2009). The introduction of non-breast milk and its potential allergen are associated with the age at which the milk is introduced and the duration of this type of feeding (Friedman et al, 2005; Lodge et al., 2015). Postponing the introduction of non-breast milk until at least four months of life can protect against asthma and atopy later in childhood (Oddy et al, 1999). Thus, the present study is in line with previous studies, showing breastfeeding as a protective factor against asthma, with 18% lower prevalence of reports of asthma symptoms at six years of age.

The results of the present study must be taken with caution since certain limitations should be considered. The report of recall data by mothers or primary caregivers may lead to information bias. In addition, some variables could have been better explored, for example, the period of breastfeeding, whether exclusive or not, and also whether one or both parents had asthma.

## 5. Final Considerations

This study observed association between the occurrence of infectious diseases in the first two years of life and the occurrence of asthma symptoms in children at six years of age. It could be concluded that the prevalence of asthma symptoms reports was 18.7% in six-year-old children. Such prevalence was found to be independently associated with reports of respiratory diseases occurrence in the first two years of life and with a family history of asthma. There was also a statistically lower asthma prevalence in breastfed children in the first two years of life. It is suggested that further studies on this topic be developed, based on longitudinal designs, to better elucidate the asthma determinants in children.

## Acknowledgments

Funding: FAPESC/Brazil Grant No. 09/2015.

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