

DR. CAROLINA SANCHEZ ARANDA (Orcid ID : 0000-0002-2187-8192)

Received Date : 23-Nov-2016

Revised Date : 08-Feb-2017

Accepted Date : 21-Feb-2017

Article type : Letter to the Editor

Wheezing and the first thousand days of life

carolaaranda@yahoo.com.br

To the Editor,

There is a recent discussion on the importance of the first thousand days of a child's life. This period covers from conception to the end of the second year of life (1). Recent studies suggest that this period is an open window for interventions and that such interventions may spread to the rest of life (2,3).

Given this new paradigm, it is discussed how the environment can interfere in the development and aggravation of diseases (4). Epidemiological and clinical trial data show that events during fetal life and early years of life, especially related to nutrition and lifestyle, can promote genetic modifications and have epigenetic effects on the development of various organs, increasing susceptibility to various diseases (5).

Most children with asthma develop symptoms such as wheezing early in life. Asthma is the most common chronic non-communicable disease (NCD) in childhood, and its increased prevalence may reflect a vulnerability in the development of the immune system, especially due to changes in modern life

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12710

This article is protected by copyright. All rights reserved.

style. Environmental factors can interfere in the pathogenesis of asthma since the beginning of life and even before birth (6).

The *Estudio Internacional de Sibilancias en Lactantes (EISL* – International Study of Wheezing in Infants) is designed to study the impact of wheezing in the first year of life, determining its prevalence and factors associated with it, using a written standard questionnaire (WQ – EISL) (7).

The aim of this study was to evaluate the factors associated with wheezing in an evolutionary way, in the same population, valuing the period called the first thousand days of life.

Three Brazilian cities – São Paulo, Cuiaba, and Maceio – participated in this evaluation. All cities applied the WQ-EISL to parents or caregivers of infants 12 to 15 months (Phase 1). After a period of 18 months, a summarized WQ was applied to a representative and randomized sample of the original group in order to evaluate the factors that had an association with persistent wheezing. This step was called EISL Phase 2 and was the first time the EISL, which was designed as a cross-sectional study, was performed as a prospective study.

The number of participants at Phase 2 of the study was calculated from the total sample of Phase 1. Simple randomization (Excel, 2010) was carried out so that everyone had the same probability of being selected. For this new sample to have a 90% power, it was established that 20% of the original sample agreed to participate in this new study. The PASS 13 software (*Power Analysis and Sample Size*) – NCSS) was used for the calculation of the sample.

Infants were divided per the frequency of wheezing episodes: occasional (OW, one to two episodes) and recurrent (RW, three or more episodes). The prevalence of wheezing between Phases 1 and 2 was calculated by the Mc Nemar test. The following groups were defined according to patterns of wheezing:

- 1) Group “Persistent”: children with RW during the first year of life and during follow-up,
- 2) Group “Worsening”: non-wheezing children or OW during the first year of life but with RW during follow-up,

- Accepted Article
- 3) Group "Improvement": children with RW during the first year of life but with no wheezing or only OW during follow-up,
 - 4) Group "Healthy": non-wheezing children or with OW during the first year of life and without wheezing during follow-up.

A model for odds ratio (OR) through multinomial regression was performed (Model 1), and the summation of the "Healthy" and the "Improvement" groups was considered the dependent variable, with the goal of identifying risk and protective factors associated with persistent wheezing.

After this step, a new logistic regression model (Model 2) was conducted to evaluate the factors that were identified as relevant in EISL Phase 1 for the summation of the "Persistent" and "Worsening" groups (*versus* "Healthy" and the "Improvement" groups).

The data was statistically analyzed using the *Statistical Package for the Social Sciences for Windows* - SPSS - version 18.0. To determine the association between risk factors of categorical nature with wheezing, Chi-square or Fisher's exact tests were used. For all statistical tests, a 5% significance level was used.

All participating centers had the approval of their local Research Ethics Committees.

Randomization included 25% of the sample (n=802). There was a loss of 3.9% (n=125) due to refusal or not getting new contact information. Information of 677 children (21.1%) who participated in Phase 1 (n=3,208) of the three centers were analyzed, which is a sample considered representative.

The prevalence of wheezing was not significantly different between the phases 1 and 2 ($p=0.139$). Participants who never had episodes of wheezing represented 73.0% (n=2,342) in Phase 1 and 69.0% (n=467) in Phase 2. For OW, proportions were 12.0% (n=382) and 14.6% (n=99). For RW, proportions were similar, with 15.1% (n=484) and 16.4% (n=111) in Phases 1 and 2

respectively. The mean age in months in Phase 1 was 13.7, while in Phase 2 it was 30.2.

The "Persistent" group consisted of 49 preschool children (7.2%). The "Worsening" group consisted of 62 (9.2%); the "Improvement" group consisted of 53 (7.8%), and the "Healthy" group consisted of 513 (75.8%) participants.

There were no significant differences among the four groups (EISL phase 2) in relation to gender ($p=0.513$), day care attendance ($p=0.239$), consumption of processed products ($p=0.315$), and the presence of animals at home ($p=0.098$).

The final model (Model 1) defined factors associated with wheezing (Table 1). In it, it could be observed that the presence of four or more upper respiratory tract infections (URTI) in the last twelve months, the diagnosis of allergic rhinitis, and history of pneumonia were significantly associated with the "Worsening" and "Persistent" groups.

Participants of the "Worsening" ($n=62$) and "Persistent" ($n=49$) groups totaled 111 preschoolers. A new logistic regression model (Model 2) using the EISL Phase 1 data, was conducted to evaluate the factors associated with the risk of recurrent wheeze (Table 1).

A large proportion of patients with asthma develop symptoms in the first thousand days of life, but there is great difficulty in diagnosis, especially by confusion with other diseases such as pneumonia, foreign body aspiration, and malformations (8).

Asthma is a complex hereditary disease influenced by the environment and modified by exposure to various substances. Increasing evidence indicates that childhood respiratory diseases may have an early schedule, being influenced by different environmental factors such as allergens, viruses, pollution, and smoking. The diagnosis of asthma cannot be easily established in this age group, but different studies point to a strong association between RW and future asthmatics (9).

The identification of children who will continue wheezing is extremely necessary. Knowing the factors associated with persistent states perfects the treatment of each patient. The identification of modifiable factors infers the possibility of changing the course of the disease, especially if interventions happen in early childhood (10).

The EISL is an international multi-center study with participation of countries from Latin America and Europe. The compilation of the results of Phase 1 revealed that 20.3% of the 30,093 investigated infants presented RW. Regarding associated factors, presenting early URTI and attending day care were the factors associated with an increased risk of RW (9).

When performing the two regression models, preschool children with higher chances of developing asthma ("Worsening" and "Persistent" groups) already presented, in the first year of life, frequent upper respiratory tract infection, the diagnosis of allergic rhinitis, and history pneumonia as the factors associated with the risk of developing recurrent wheezing.

Infections, especially viral infections, are common in children, particularly in the first year of life. This can happen due to the immaturity of the immune system. Infections by respiratory syncytial virus, rhinovirus, and influenza may progress to recurrent episodes of wheezing. Several studies demonstrate the robust relationship between rhinovirus infections and the subsequent development of asthma (8).

The role of bacteria in the development of asthma is still controversial. However, bacterial infections can contribute to airway inflammation, worsening asthma symptoms. There seems to be a relation of the microbiota or the airways with clinical and inflammatory characteristics of asthma. The association between pneumonia and RW may be due to shared pathophysiology or the misdiagnosis between the two conditions (9). Moreover, changes in the intestinal flora seem to contribute and decrease the chances for the development of asthma (10).

The Asthma Predictive Index (API), designed from the prospective study *Tucson Children's Respiratory Study* proposed to diagnose future asthmatics

among infants with recurrent wheezing. The presence of allergic rhinitis is an important criterion of this index (8) and was one of the factors with the greatest impact on this assessment.

Our study had some limitations. The use of a questionnaire with questions that depend on the memory of the parents may generate an information bias, although some studies show that parents are able to remember diseases of their children (9). Another limitation was that this group of children did not conduct a follow-up with physical and complementary exams, and only answered the questionnaire at two different times, wasting the opportunity to collect new and more accurate data.

It can be concluded that frequent URTI, diagnosis of allergic rhinitis, and history of pneumonia can be considered predictors of future asthma in this population. The initiative of the 1000 days should extrapolate nutritional guidelines and seek new forms of intervention as different vaccines against respiratory viruses, identification of biomarkers to aid in the early diagnosis of allergic diseases, and research on the differences in the microbiome of asthmatics and healthy children. The modification of environmental factors and anticipated and personalized treatment may change the course of asthma in childhood.

Table 1 – Odds ratio estimates (OR) of the final model of multinomial regression (Model 1) and logistic regression (Model 2).

Factors	Model 1						Model 2		
	"Worsening" Group n=62			"Persistent" Group n=49			"Persistent" + "Worsening" EISL 1 n=111		
	OR	IC95%	p	OR	IC95%	p	OR	IC95%	p
Allergic rhinitis diagnosis	5.22	(2.95 - 9.25)	<0.001	3.50	(1.82 - 6.71)	<0.001	2.50	(1.32 - 4.75)	0.005
History of pneumonia	2.46	(1.11 - 6.63)	0.04	3.91	(1.5 - 10.14)	0.005	3.31	(1.45 - 7.57)	<0.001
4 or more URTIs*	5.76	(2.74 - 12.13)	<0.001	6.00	(2.6 - 13.83)	<0.001	4.42	(3.22 - 10.45)	<0.001

Model 1 and Model 2: Reference category of the dependent variable: "Healthy"(n=513) + "Improvement"(n=53) Groups (total n=566).
 Model 2: "Persistent" + "Worsening" (*adjusted odds ration*): history of pneumonia, parental history of asthma, maternal smoking, passive smoking, URTI history before 3 months of age, history of four or more episodes of upper respiratory infections in the first year of life, C-section birth, mother with paid work, diagnosis of allergic rhinitis, according to the EISL Phase 1 data.
 *URTIs: upper respiratory tract infections.

- Accepted Article
- 1- Bhutta ZA, Ahmed T, Black RE, Cousens S, Dewey K, Giugliani E, et al. What works? Interventions for maternal and child under-nutrition and survival. *Lancet*. 2008;371:417-40.
 - 2- da Cunha AJ, Leite AJ, de Almeida IS. The pediatrician's role in the first thousand days of the child: the pursuit of healthy nutrition and development. *J Pediatr (Rio J)*. 2015;91:S44-51.
 - 3- Criss S, Woo Baidal JA, Goldman RE, Perkins M, Cunningham C, Taveras EM. The Role of Health Information Sources in Decision-Making Among Hispanic Mothers During Their Children's First 1000 Days of Life. *Matern Child Health J*. 2015;19(11):2536-43.
 - 4- Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, Uauy R; Maternal and Child Nutrition Study Group. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet*. 2013;382(9890):427-51.
 - 5- Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359(1):61-73.
 - 6- Prescott SL. Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases. *J Allergy Clin Immunol*. 2013;131(1):23-30.
 - 7- Mallol J, García-Marcos L, Aguirre V, Martinez-Torres A, Perez-Fernández V, Gallardo A, et al. The International Study of Wheezing in Infants: questionnaire validation. *Int Arch Allergy Immunol*. 2007;144(1):44-50.
 - 8- Martinez FD. The connection between early life wheezing and subsequent asthma: The viral march. *Allergol Immunopathol (Madr)*. 2009;37(5):249-51.
 - 9- Aranda CS, Wandalsen G, Fonzar L, Bianca AC, Mallol J, Solé D. Risk factors for recurrent wheezing--International Study of Wheezing in Infants (EISL) phase 3. *Allergol Immunopathol (Madr)*. 2016;44(1):3-8.
 - 10- Anderson WC 3rd, Szefer SJ. New and future strategies to improve asthma control in children. *J Allergy Clin Immunol*. 2015;136(4):848-59.