

Wheezing and low birth weight

To the Editor,

Although controversial, low birth weight is pointed out by several studies as a risk factor for wheezing and asthma in children (1). This group of children is very heterogeneous, being composed largely of newborns with intrauterine malnutrition and premature infants. Advances in perinatal care have significantly increased survival of these children in recent decades and, coupled with the increase in the number of multiple births, make this group of infants more numerous (2). The largest number of infants born with low birth weight may have contributed to the increase in asthma prevalence observed in various parts of the world during this period.

The *Estudio Internacional de Sibilancias en Lactantes* (EISL) was designed to study the impact of wheezing in the first year of life, determining its prevalence and associated factors, using standardized and validated questionnaire (QE-EISL) (3).

A limited number of studies have examined the impact of low birth weight on respiratory symptoms and diagnosis of asthma in early life. The objective of this study was to describe the prevalence of asthma and wheezing during the first year of life in infants born with low birth weight and to evaluate, in this group, differences between those born with more and less than 2,000g.

Parents of infants aged between 12 and 15 months, residents in six Brazilian capital cities - Belém, Belo Horizonte, Cuiabá, Curitiba, Recife, and São Paulo - have participated in interviews between 2005 and 2010, answering

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.12320

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the QE-EISL. In accordance with the study recommendations, each center included at least 1,000 infants (3).

The infants were divided primarily into two groups, according to World Health Organization (WHO): those with birth weight equal to or higher than 2,500g (adequate weight or AW) and those with birth weight of less than 2,500g (low birth weight or LBW). The LBW group was further divided into a group formed by infants with birth weight between 2,000 and 2,499 grams (LBWa) and another group for those weighing less than 2,000 grams (LBWb) at birth.

Regarding to the report of wheezing episodes, all infants who had at least one episode formed the wheezing group, and were divided according to the frequency of episodes: recurrent wheezing (RW, three or more episodes) and severity: severe recurrent wheezing (SRW, six or more episodes or three or more episodes of wheezing associated with hospitalization).

The data obtained were statistically analyzed using SPSS - version 18.0. Chi-square tests were used to determine the association between risk factors of categorical variable with wheezing. Logistic regression was used to evaluate the effects of associated factors on wheezing and low birth weight. For all statistical tests, a significance level of 5% was used. All participating centers had approval from the Local Ethics Committees.

A total of 12,582 questionnaires were considered valid. Of these, 11,411 (90.7%) infants were born with adequate weight and 1,171 (9.3%) with low weight, 874 in the LBWa group and 297 in the LBWb group.

The characteristics of infants, stratified by birth weight, are found in Table 1. Female gender, passive smoking, and maternal smoking during pregnancy were more frequent among infants of the low weight group as well as the first upper respiratory tract infection (URTI) before six months of age (Table 1).

Table 2 shows the clinical characteristics of each group of infants according to birth weight, with the OR adjusted by gender, gestational and passive smoking, breastfeeding, and history of early and frequent upper respiratory infections. It can be observed that, compared to adequate weight birth infants, infants of the low birth weight group had a higher frequency of wheezing in the first year of life (49% vs 44%), recurrent wheezing (28% vs

22%) and severe recurrent wheezing (21% vs 13%), as well as hospitalizations for wheezing, pneumonia, hospitalizations for pneumonia, visits to the emergency units and the diagnosis of asthma.

In comparisons between the two subgroups of infants born with low birth weight (Table 2), significant differences in most of the variables associated with greater severity of wheezing can be observed, such as RW (38% vs 25%), SRW (30% vs 18 %), hospitalizations for wheezing (21% vs 11%) and hospitalizations for pneumonia (17% vs. 9%).

The association between low birth weight and asthma has been studied and appears to be stronger among younger children, with a progressive decrease in its intensity with age. A recent meta-analysis found that children with low birth weight had 16% greater risk to develop asthma than those born with adequate weight (1). However, the results were heterogeneous, possibly reflecting differences in the assessed populations, the study design, the ages of the children, and in the definition of low birth weight (1). In a recent publication, international data from ISAAC phase III study was used to evaluate the connection between low birth weight and asthma, including over 160,000 children aged 6 and 7 years of age in 26 countries (4). In this study, low birth weight was significantly associated to current asthma (OR: 1.2 [1.1 – 1.3]), severe asthma symptoms (OR: 1.4 [1.3 - 1.6]) and diagnosis of asthma (OR: 1.3 [1.2 - 1.4]) (4).

A similar finding can be observed in the present study, in which a clear association between low birth weight and respiratory symptoms in the first year of life was noted. It was also observed that the relation between birth weight and wheezing was strongest in outcomes related to severity, both in the comparison of infants with low and adequate birth weight and between the two subgroups of infants born with low birth weight (Table 2).

The causes of the connection between low birth weight and asthma/respiratory symptoms are likely to be multiple and not yet fully known. Low birth weight is strongly related to prematurity and intrauterine growth restriction. These two factors are related to impairment in lung development and deficit in lung function (5).

Accepted Article

It is increasingly recognized that early life events during pregnancy and the first years of life can promote genetic modifications and have epigenetic effects on growth and development of several organs, favoring the development of chronic diseases such as asthma (6).

Viruses and respiratory infections play an extremely important role in the development and maintenance of wheezing and respiratory symptoms in young children. In this study, a higher prevalence of early upper respiratory tract infections (URTI), pneumonia, and hospitalizations for pneumonia were observed in the LBW group. It has been reported that infants born with low birth weight are more susceptible to respiratory infections, possibly associated with changes in the immune system (7).

It is worth noting that the association between low birth weight and asthma can be complicated due to several other factors related to both the development of asthma and the low birth weight, such as maternal smoking during pregnancy and passive smoking. However, this relation observed in this study remained significant even after controlling these variables.

Family history of asthma has been associated with low birth weight in many studies. Complications during pregnancy and childbirth of asthmatic pregnant women, especially in those without treatment, could increase the risk of premature births and low birth weight (8). This association, however, is not unanimous and was not observed in this study.

The rapid early weight gain frequently observed in infants born with low birth weight, have also been described as a risk factor for the development of childhood asthma. The mechanisms involved in this association are not well known, but there is evidence of hormonal, immunological, and inflammatory factors (9).

This study has some limitations. The use of referred information about weight may have introduced inaccuracies. Gestational age at birth was not asked and, thus, it was not possible to distinguish low birth weight secondary to prematurity from low birth weight secondary to intrauterine growth restriction. Finally, the medical diagnosis of asthma in the first year of life is difficult to be established and should be interpreted with caution.

In conclusion, we observed a greater prevalence, severity, and morbidity of wheezing in the first year of life in infants born with low birth weight. In the low birth weight group, an increased severity and morbidity was observed among infants born with less than 2,000g, indicating an inverse and increasing association of the severity of wheezing in the first year of life with the birth weight. The high prevalence of respiratory problems in infants born with low birth weight clearly indicates that they should receive careful attention and be closely monitored during the first year of life. Initiatives to reduce passive and pregnancy smoking, as well as better prenatal care, can help in the prevention of low birth weight and in the reduction of respiratory morbidity in early childhood.

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Table 1 - Clinical characteristics of infants in the first year of life, separated by birth weight: Low birth weight (LBW, less than 2,500g) and adequate birth weight (AW, equal to or greater than 2,500g).

Characteristics	LBW	AW	Total	p ¹
	(N=1,171)	(N=11,411)	(N=12,582)	
	n (%)	n (%)	n (%)	
Male	530 (45.2)	5,812 (50.9)	6,342 (50.4)	<0.001*
Smoking during Pregnancy	173 (14.8)	1,101 (9.7)	1,274 (10.1)	<0,001*
Passive Smoking	496 (42.4)	4,162 (36.5)	4,658 (37.0)	<0.001*
Family history of asthma	296 (25.3)	2,739 (24.1)	3,035 (24.1)	0.312
Maternal history of asthma	87 (7.4)	841 (7.4)	928 (7.4)	0.926
Paternal history of asthma	56 (4.8)	531 (4.7)	587 (4.7)	0.830

History of siblings with asthma	58 (4.9)	502 (4.4)	560 (4.5)	0.373
Breastfeeding $\geq$ 4 months	658 (56.1)	7,855 (68.8)	8,513 (67.6)	<0.001*
URTI - more than 5 episodes/year	423 (36.1)	3,885 (34.0)	4,308 (34.2)	0.104
URTI - first one before 6 months of age	849 (72.5)	8,004 (70.1)	8,853 (70.4)	0.031*
Attends day care in the 1st year of life	200 (17.1)	2,031 (17.8)	2,231 (17.7)	0.530

[†] Descriptive level of the chi-square test. URTI: Upper respiratory tract infections. * Statistically significant results

Table 2 - Personal and clinical characteristics of each group (§) of infants in the first year of life, separated according to birth weight **.

Variables	Birth weight				Low birth weight			
	LBW	AW	p	OR (95%CI)	LBWa	LBWb	p	OR (95%CI)
	(N=1,171)	(N=11,411)			(N=874)	(N=297)		
Wheezing once- n(%)	579 (49.4)	4,991 (43.7)	0.03*	1.2 (1.0-1.3)	411 (47.0)	168 (56.6)	0.23	1.2 (0.9-1.6)
Recurrent wheezing (RW) - n(%)	331 (28.3)	2,488 (21.9)	0.001*	1.3 (1.1-1.5)	217 (24.9)	114 (38.4)	0.005*	1.6 (1.1-2.2)
Severe recurrent wheezing (SRW)- n(%)	248 (21.2)	1,491 (13.1)	<0.001*	1.7 (1.4-2.0)	159 (18.3)	89 (30.0)	0.005*	1.6 (1.2-2.3)
Visits to the emergency service- n(%)	393 (33.6)	3,148 (27.6)	<0.001*	1.2 (1.1-1.4)	275 (31.5)	118 (39.7)	0.48	1.1 (0.8-1.5)
Hospitalization for wheezing- n (%)	159 (13.6)	897 (7.9)	<0.001*	1.7 (1.4-2.0)	96 (11.0)	63 (21.2)	0.006*	1.7 (1.2-2.5)
Diagnosis of asthma- n(%)	114 (15.8)	853 (12.6)	0.04*	1.3 (1.0-1.6)	76 (14.6)	38 (18.6)	0.10	1.5 (0.9-2.3)
Pneumonia- n(%)	211 (18.0)	1,496 (13.1)	<0.001*	1.4 (1.2-1.6)	143 (16.4)	68 (22.9)	0.20	1.3 (0.9-1.8)
Hospitalization for wheezing- n(%)	130 (11.1)	856 (7.5)	<0.001*	1.5 (1.2-1.8)	81 (9.3)	49 (16.5)	0.05*	1.5 (1.0-2.3)

(§) LBW: weight <2500g; AW: ≥2500g weight; LBWa: weight between 2000g and 2499g; LBWb: weight <2000g. p - Descriptive level of the chi-square test or exact Fisher. * Statistically significant results ** OR and p adjusted based on gender, gestational and passive smoking, breastfeeding, and history of early and frequent upper respiratory tract infections (URTI).