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Effects of low birth weight on lung function in children and adolescents: A review

Pedro Martins Lima Neto[1], Antônio Marcus de Andrade Paes[2], Raina Jansen Cutrim Propp Lima[3], Rosângela Fernandes Lucena Batista[4], Alcione Miranda dos Santos[4], Vanda Maria Ferreira Simões[4]

[1]Universidade Federal do Maranhão, Imperatriz, MA, Brasil.
[2]Programa de Pós-graduação em Ciências da Saúde, Universidade Federal do Maranhão, São Luís, MA, Brasil.
[3]Instituto Federal de Educação, Ciência e Tecnologia do Maranhão, Açailândia, MA, Brasil.
[4]Programa de Pós-graduação em Saúde Coletiva, Universidade Federal do Maranhão, São Luís, MA, Brasil.

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Abstract— *In this study, we aimed to carry out an integrative review of studies that assessed the effects of low birth weight on pulmonary function in children and adolescents. A total of 18 out of 64 retrieved articles were included in this review. The sample size totaled 3,409 children and adolescents distributed into case and control groups. Spirometric assessment was held at ages ranging from 5 to 18 years. In three studies, assessments were performed more than once at different ages. Most studies were carried out in Europe. In all studies, at least one of the spirometric measurements was reduced, with end-expiratory volume in one second being the most frequent. Low birth weight appears to negatively influence lung function in children and adolescents, and the effects of this impairment may be long-lasting and persist through other stages of life.*

I. INTRODUCTION

There are 2.9 million neonatal deaths worldwide annually, whose main causes are infections, intrapartum conditions and complications related to preterm birth. More than 80% of those deaths occur in low birth weight newborns, from which two thirds are born preterm and one third are small for gestational age (1). Children weighing less than 2,500g are considered with low birth weight (LBW), regardless of their gestational age (2). According to a recent systematic review, worldwide prevalence of LBW in 2015 was 14.6%, showing a slight decrease as compared to 17.5% in 2000 (3). LBW is an important public health indicator, particularly in places where it is difficult to accurately assess the gestational age (4). Birth weight is also an important measure of the newborn's health and an important predictor of the risk of later-in-life illness. LBW increases the chances of developing health issues, as consequence of poor maturation of the organs, higher mortality, greater long-term vulnerability, neuropsychomotor development deficit and impaired school development (5). This influence of birth weight on the onset of diseases at later stages of life has not yet been fully clarified, but it is strongly supported by the concept of the developmental origins of health and disease (DOHaD) (6).

In Brazil, although neonatal mortality had fallen by 34% between 2000 and 2010, it still accounts for about 70% of deaths in the first year of life, with 26% occurring in the first 24 hours of life. The main factors associated with mortality on the first day of life are LBW and preterm birth (7). Data from the survey "Born in Brazil", a national hospital-based study conducted between February 2011 and July 2012, including 24,197 puerperal women and their newborns, concluded that birth weight below 1,500g was one of the indicators of neonatal morbidity *near miss*, able to identify situations associated with high risk of neonatal death (8).

Among the many outcomes of LBW, a recent study assessed lung function in adults born with very low birth weight and showed that respiratory problems are one of the most frequent health issues in the neonatal period, which persist among survivors and constitute common causes of morbidity in childhood and adolescence (9). Lung function in low birth weight or extremely low birth weight newborns is linked to a physiological response that triggers a mechanical impairment, with changes in the elastic properties of the lungs, resulting in reduced global muscle strength, including diaphragmatic, with consequent change in lung volumes and capacities (10). In this sense, lung function tests are important tools to assess the respiratory system (11). Among these measures, the spirometry test is a good and affordable alternative to assess lung volumes and capacities (12).

Therefore, assuming that newborns with low birth weight may have developmental issues (13) and that they seemly have less lung reserve compared to those born with appropriate weight (14), determining whether LBW is associated with altered lung function in childhood and adolescence is of paramount importance for the development of public health strategies for health promotion and prevention of disorders related to reduced lung function. Thus, the goal of this review was to gather data to characterize the effects of LBW on lung function in children and adolescents.

II. MATERIAL AND METHODS

This report consists of an integrative review carried out through a search in the Scopus, PubMed, SciELO and LILACS electronic databases. Articles in all languages were selected, with no filter for publication year. In order to achieve the goal of this report, the following guiding question was created: Does LBW interfere with lung function in childhood and adolescence? The search used to select the articles was based on two keywords extracted from the Medical Subject Headings (MeSH) and searched using Boolean operators as follows: *Low birth weight* AND *Spirometry*. These descriptors should appear at least in the title and/or abstract. The search for studies was carried out from May to June 2020.

As inclusion criteria, studies that assessed lung function through spirometry in children and adolescents born with LBW were considered, according to the guidelines of the *European Respiratory Society* (ERS) and the *American Thoracic Society* (ATS) (15). The choice of the spirometry test as an assessment tool was due to the fact that it is a simple, non-invasive and easy-to-apply resource widely used to assess lung volumes and capacities (12). In addition, studies needed to have assessed at least the following spirometric variables for inclusion: forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and forced expiratory flow from 25 to 75% of lung volume ($FEF_{25-75\%}$). It is important to highlight that the classification criteria of each author regarding the definitions of birth weight were considered, as well as the normal or abnormal values regarding lung function. Conversely, case reports, meta-analyses, review studies, articles that assessed lung function using an assessment method other than spirometry, studies that also assessed the adult age group or that did not include only children and adolescents, as well as those in which there was maternal smoking during pregnancy, were excluded.

The search and the analysis of the articles were carried out with methodological rigor, independently, by two experienced reviewers, and any problem or divergence was resolved by consensus. After obtaining the search result from the databases, the titles and abstracts of the articles were read, and those that met the inclusion criteria were separated for reading in full for subsequent inclusion in a table, in order to compose the results. Information from the studies was extracted and organized as follows: name of the first author, year of publication and country where data were collected, study goals, sample size and organization into groups, stratification of birth weight, age at which children and adolescents underwent lung assessment and the main results of spirometric variables such as FEV_1, FVC and $FEF_{25-75\%}$.

III. RESULTS

The search strategy led to the retrieval of 64 articles, 36 in Scopus, 26 in PubMed, 2 in SciELO and 9 in LILACS. After reading the titles and abstracts, 25 (39.1%) articles were excluded for being duplicated in different databases and 21 (32.8%) for not meeting the inclusion criteria proposed by this study. The final sample of this review consisted of 18 (28.1%) original articles (Figure 1).

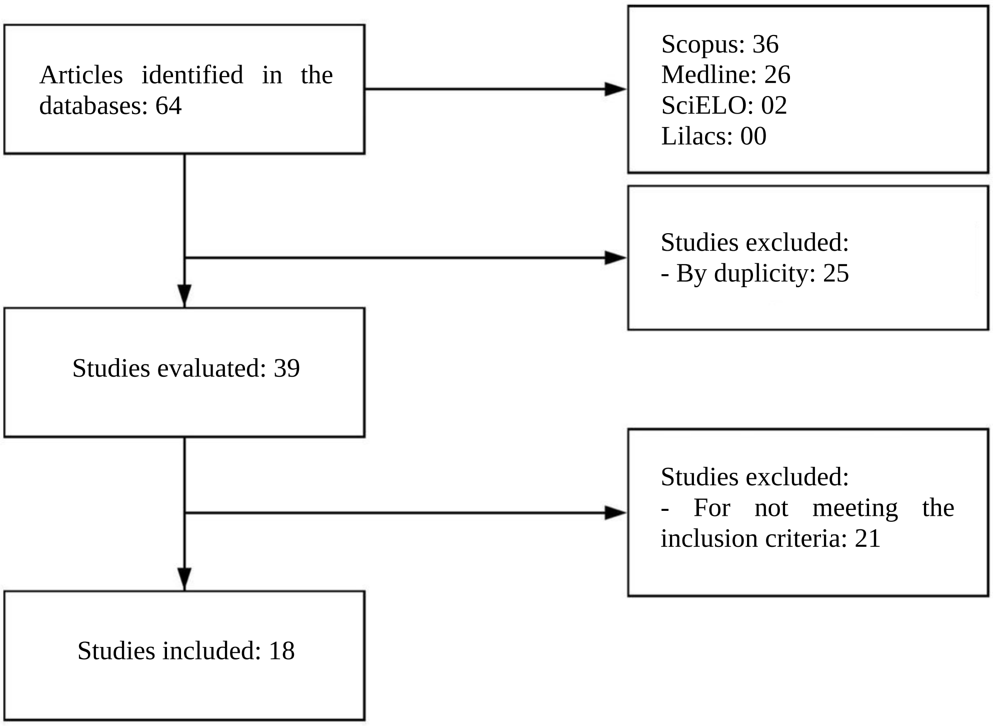

Fig.1 - Search strategy and article selection from May to June 2020

All 18 selected articles were published in English are displayed in chronological order of publication (Table 1). The sample size of the population studied in the 18 articles totaled 3,409 children and adolescents, with a distribution into case and control groups, according to gestational age, birth weight, diagnosis of any pathology, use of drugs and type of ventilatory mode. With respect to birth weight, the studies varied in three stratifications for the case groups: extremely low weight (<1,000g or <1,001g), very low weight (<1,500g or <1,501g) and low weight (<2,500g) and one for the control group: normal weight (>2,499g or >2,500g). The administration of drugs (corticosteroid therapy) and the type of ventilation mode chosen in the critical period of life of the patients were also criteria for the definition of the groups.

Table 1 – Characteristics of studies included in this review from May to June 2020

Authors, year and country	Objectives	Sample and birth weight	Assessment age	Results
Mai et al. [16], 2003, Sweden	To assess the ratio between very low birth weight (VLBW) and development of asthma, lung function and atopy.	72 VLBWG[a], <1,500g; 62 CG[b], >2,500g	12 years	Spirometric values were similar between groups.
Korhonen et al. [17], 2004, Finland	To check the influence of surfactant on lung function in schoolchildren with very low birth weight (VLBW) with and without BPD[c].	34 VLBWG[a] with BPD[c], <1,500g; 34 VLBWG[a] without BPD[c], <1,500g; 34 CG[b], >2,500g	Between 7 and 8 years	VLBWG[a] with and without BPD[c] had lower FEV_1[d] compared to CG[b].
Siltanen et al. [18], 2004, Finland	To investigate the association between atopy, wheezing and respiratory function in children born with very low birth weight compared to children born with	72 VLBWG[a], <1,501g; 65 CG[b], >2,500g	10 years	Lower FEV_1 [d], FVC[e], FEV_1 [d]/FVC[e] and $FEF_{25-75\%}$[f] values in VLBWG[a].

	normal weight.			
Korhonen et al. [19], 2005, Finland	To assess cardiovascular findings in very low birth weight schoolchildren with and without BPD[c].	34 VLBWG[a] with BPD[c], <1,500g; 34 VLBWG[a] without BPD[c], <1,500g; 34 CG[b], >2,500g	Between 7 and 8 years	VLBWG[a] with and without BPD[c] had lower FEV_1 [d] compared to CG[b].
Nixon et al. [27], 2007, United States	To determine whether postnatal exposure to dexamethasone affects lung function in children born with very low birth weight (VLBW).	38 VLBWG[a] with DEX[g], <1,501g; 30 VLBWG[a] without DEX[g], <1,501g	Between 8 and 11 years	Lower FEV_1 [d] and FVC[e] values in VLBWG[a] without DEX[g].
Broström et al. [20], 2010, Sweden	To analyze the impact of BPD[c] on lung function and the prevalence of atopy in schoolchildren.	32 VLBWG[a] with BPD[c], <1,500g; 28 VLBWG[a] without BPD[c], <1,500g	Between 6 and 8 years	Lower FEV_1 [d], FVC[e], FEV_1 [d]/FVC[e] and $FEF_{25-75\%}$ [f] values in VLBWG[a] with BPD[c].
Guimarães et al. [21], 2011, Portugal	To assess lung function and the prevalence of atopy in schoolchildren who were born with very low birth weight with or without BPD[c].	13 VLBWG[a] with BPD[c], <1,500g; 64 VLBWG[a] without BPD[c], <1,500g	Between 5 and 8 years	Spirometric values were similar between groups.
Novais et al. [22], 2012, France	To check the influence of exercise on lung function in infants born with very low birth weight.	19 VLBWG[a] with and without BPD[c], <1,500g; 20 CG[b], >2,500g	Between 8 and 10 years	Lower $FEF_{75\%}$ values in VLBWG[a] with and without BPD[c].
Nixon et al. [28], 2013, United States[xx]	To compare lung function and asthma history of adolescents born with very low birth weight with and without steroid exposure.	94 VLBWG[a] with antenatal corticosteroid therapy, <1,500g; 94 VLBWG[a] antenatal corticosteroid therapy, <1,500g	14 years	Spirometric values were similar between groups.
Kwinta et al. [23], 2013, Poland	To determine whether ELBW babies are at increased risk of developing allergic and respiratory symptoms and the possible risk factors.	89 ELBWG[h], <1,000g; 40 CG[b], >2,500g	Between 6 and 7 years	Lower FEV_1 [d], FVC[e] and $FEF_{50\%}$ values in ELBWG[h].
Lista et al. [24], 2014, Italy	To investigate lung function in very low birth weight (VLBW) schoolchildren without BPD[c].	13 ELBWG[h] who received HFOV[i], <1,000g; 12 ELBWG[h] who received VG[j], <1,000g	Between 6 and 7 years	In both groups, FEV_1 [d] values were lower.
Hove et al. [25], 2014, Germany	To assess and compare lung function in very low birth weight prematurely born children with and without BPD[c] born in the surfactant era.	28 VLBWG[a] with BPD[c], <1,500g; 28 VLBWG[a] without BPD[c], <1,500g	Between 6 and 12 years	Lower FEV_1 [d], FVC[e] and $FEF_{50\%}$ values in VLBWG[a] with BPD[c].
Hirata et al. [30], 2015, Japan	To assess lung function in children born with extreme low birth weight and to identify perinatal determinants associated with lung function.	201 ELBWG[h] of a Japanese cohort study, <1,001g; 455 ELBWG[h] of the general population,	Between 7 and 9 years	There was a decrease in FEV_1 [d], FVC[e], FEF_{25}% and $FEF_{50\%}$ in ELBWG[h] of the Japanese cohort

		<1,001g		study.
Gonçalves et al. [29], 2016, Brazil	To assess prevalence, spirometry and risk factors for asthma in schoolchildren who were very low birth weight newborns with and without BPD[c].	18 VLBWG[a] with BPD[c], <1,500g; 36 VLBWG[a] without BPD[c], <1,500g	Between 7 and 11 years	Spirometric values were similar between groups.
Doyle et al. [33], 2016, Australia	To compare the changes in spirometry at the ages of 8 and 18 years in low birth weight premature infants with normal birth weight full-term infants.	240 ELBWG[h] at the age of 8 years, <1,000g; 208 CG[b] at the age of 8 years, >2,499g; 209 ELBWG[h] at the age of 18 years, <1,000g; 154 CG[b] at the age of 18 years, >2,499g	At the ages of 8 and 18 years	Decrease in FEV_1 [d], FVC[e], FEV_1 [d]/FVC[e] and $FEF_{25-75\%}$ [f] ratio of ELBWG[h] at both ages.
Fortuna et al. [26], 2016, Italy	To study the lung function of a cohort of premature infants with extreme low birth weight (ELBW) in the post-surfactant era.	28 ELBWG[h] with BPD[c], <1,000g; 20 ELBWG[h] without BPD[c], <1,000g; 27 CG[b], >2,499g	At the ages of 8 and 12 years	Decrease in FEV_1 [d], FVC[e], FEV_1 [d]/FVC[e] and $FEF_{25-75\%}$ [f] ratio in ELBWG[h] with BPD[c] compared to CG[b].
Hirata et al. [31], 2017, Japan	To assess lung function and long-term respiratory outcomes in survivors with extreme low birth weight (ELBW).	89 ELBWG[h] of a Japanese cohort study, <1,001g; 78 ELBWG[h] of the general population, <1,001g	At the ages of 8 and 12 years	Decrease in FEV_1 [d] and FEV_1 [d]/FVC[e] ratio in ELBWG[h], showing a worsening with advancing age.
Anuntaseree et al. [32], 2019, Thailand	To investigate the determinants of lung function in Thai children.	892 LBWG[l], <2,500g	8 years	Reduction in FEV_1 [d] /FVC[e] and $FEF_{25-75\%}$ [f] ratio in patients who developed asthma.

[a]**:** group with very low birth weight newborns.
[b]**:** control group with full-term newborns.
[c]: bronchopulmonary dysplasia.
[d]: forced expiratory volume in one second.
[e]**:** forced vital capacity.
[f]**:** forced expiratory flow from 25 to 75% of lung volume
[g]**:** Dexamethasone.
[h]**:** group with extremely low birth weight newborns.
[i]**:** high frequency oscillatory ventilation.
[j]**:** ventilation guaranteed by assisted/controlled mode (volume guarantee).
[l]**:** group with low birth weight newborns.

The main common characteristic among the studies was the ratio between LBW and lung function. Prematurity and bronchopulmonary dysplasia (BPD) were also frequent among participants and were considered as selection criteria for the composition of some groups. In all studies, children who were born preterm were included in at least one of the groups and BPD was studied as exposure in eight (44.4%) of them.

Regarding the places of the surveys, 11 (61.1%) were carried out in the European continent (16-26), 3

(16.7%) in the American continent (27-29), 3 (16.7%) in the Asian continent (30-32) and 1 (5.5%) in Oceania (33). The fact that the studies were based on the ERS and ATS guidelines (15) allow for greater standardization of spirometric measurements, but the heterogeneity of the samples, especially with regard to gestational age, age at spirometric assessment and other characteristics for the composition of the groups, limits us from making some comparisons in this regard.

The studies followed different patterns with regard to age for the assessment of lung function through spirometry, which could vary between 5 and 18 years of age. In order to follow-up the evolution of spirometric measurements, Doyle et al. (33), Fortuna et al. (26) and Hirata et al. (31) undertook the test in more than one time at different ages.

In most studies, there was a reduction of at least one value in spirometric measurements, with FEV_1 being the most frequent, followed by FVC and $FEF_{25-75\%}$. Even though there was no statistical standardization in the way the data was analyzed and exposed by the different studies, the significance level based on the p-value ($p<0.05$) was considered by all. From this perspective, some studies showed highly significant ratios and some deserve to be highlighted, such as Broström et al. (20), Kwinta et al. (23), Doyle et al. (33), Fortuna et al. (26) and Hirata et al. (31), which showed p value <0.001. In other studies, the results of spirometric measurements could not be supported by the significance level. In Lista et al. (24), in both groups, there was a reduction in FEV_1 with p=0.1; and in Anuntaserre et al. (32), FEV_1/FVC ratio indicated a downward trend, with p=0.02.

Spirometric values were similar between groups and did not show significant differences in four studies, which are: Mai et al. (16), Guimarães et al. (21), Nixon et al. (28) and Gonçalves et al. (29). Only in the study by Anuntaserre et al. (32), there was no presence of the control group. In this case, the goal of the authors was to investigate which factors would influence lung function throughout development up to 8 years of age. Table 1 shows the characteristics of each of the articles.

IV. DISCUSSION

The concept for the developmental origins of health and disease points out that insults occurring at early stages of development (13,34), such as LBW, would be related to certain patterns of disease and health throughout life, including worse lung function (35,36). When assessing the association of these two variables, LBW and lung function in children and adolescents, it was possible to identify consistent findings that are in line with the literature, as described below.

LBW is commonly related to preterm birth (4), with intrauterine growth restriction or both situations (37), and is a strong influence on the morphological and functional development of the lungs and other organs (5). Colin et al. (38) argue that extremely preterm newborns are born with less developed alveoli, thicker alveolar walls, and decreased gas exchange area, which result in functional abnormalities at birth and throughout life.

In this context, the physiological response triggers a mechanical impairment with changes in the elastic properties of the lung, which results in a reduction in global muscle strength, including diaphragmatic, with a consequent change in lung volumes and capacities (10). Such information may explain the reason for the positive association of LBW with lung function in children and adolescents found in most of the articles included in this review (17-20, 22-27, 30-33), where there was a reduction of at least one of the main spirometric values (VEF_1, FVC and $FEF_{25-75\%}$) when compared to group control.

Siltanen et al. (18) point out that the fact that there is a reduction in spirometric values in this population indicates that the airways may be obstructed, with air trapping and a possible reduction in total lung capacity. Airway obstruction is also reported by Doyle et al. (33), who indicate a worsening of the condition over time, between 8 and 18 years old, and suggest that it is unlikely that these individuals will reach a normal peak of airway growth by the age of 20, which would be expected in the normal population. Still addressing the effects of LWB exposure, the results of the follow-up of the Isle of Wight birth cohort, located in England, showed that higher birth weight was significantly associated, directly or indirectly, with higher FEV_1, FVC and $FEF_{25-75\%}$ in adolescents aged 18 years (35). The fact that there is clinical worsening from childhood to adolescence demonstrates the need for intervention and follow-up throughout life.

On the other hand, some studies have shown that LBW was not significantly associated with lower spirometric values. In two of these studies (28,29), the findings overlap with the main goal and suggest alterations in lung function. The composition of the groups in the study by Gonçalves et al. (29) was based on the presence or absence of BPD; but, in adolescents who developed asthma, there was a decrease in $FEF_{25-75\%}$. In Nixon et al. (28), adolescents exposed to steroids with birth weight <1,000 grams had a 4.5 times greater chance of airway obstruction.

The studies included in this review showed great heterogeneity in the composition of the samples and were carried out in different countries and continents. According to Stanojevic et al. (39), little is known about the potential influence of specific characteristics, such as sex, weight, height, ethnicity on lung function in different populations. The same authors add that arbitrary differences in the way lung function is expressed and interpreted can imply poor patient management and make it difficult to understand the overall burden of lung disease (39).

In order to assess lung function, all studies used spirometry following the ERS and ATS guidelines (15). Spirometry can be performed with children from 2.5 years of age, as long as they have normal cognitive and neuromotor functions; but, for the test to be successful, they must be well oriented and trained beforehand (40). Although this test is indicated for young patients, it is an effort-dependent assessment, which requires understanding and cooperation from the assessed individual, which can cause difficulties in younger individuals (10).

In view of this scenario, in future studies, other tests such as volumetric capnography can be used to detect pulmonary dysfunctions (41). It is a simple and inexpensive test, easy to apply and that does not require forced maneuvers as is the case with spirometry, and can also be applied in younger individuals. Despite the positive characteristics, there is still a lack of standardization to analyze the data and a scarcity of publications, especially in the pediatric age group (11,41).

Only one of the selected studies was developed in Brazil (29). Despite this result, it is possible to follow the growing interest of national research in identifying the cause of chronic diseases and the epidemiology of the life cycle at early stages, as shown in a recent publication on Brazilian cohorts initiated in the prenatal period or at birth (42). These studies should be on the agenda of developing countries as a way of identifying causality, strengthening and expanding the epidemiology of the life cycle.

Accordingly, more follow-up surveys that assess the individual at different times in life are needed. This study was able to answer little explored questions, such as the association of LBW with lung function in childhood and adolescence, and could contribute to causality studies within the universe of DOHaD studies. This study will also serve as a starting point for further research to be developed in the area, increasing knowledge and interdisciplinary actions.

This study had limitations due to the lack of methodological standardization of the selected articles, mainly with regard to the heterogeneity of the samples and composition of the case and control groups. Another limitation was the impossibility of accessing the entire scientific production on the subject due to the need to restrict the search by means of descriptors. Regarding its strengths, one can cite the freedom in the selection and choice of articles in any language and year of publication, with the purpose of covering the largest number of publications.

V. CONCLUSION

This work allowed us to analyze studies published in journals from several countries around the world and to conclude that there was an association between LBW and lung function in children and adolescents. These effects may be long-lasting and persist even after the peak of normal airway growth. Spirometry proved to be a test capable of assessing and following-up lung volumes and capacities throughout life. Even so, future investigations on the association between birth weight and lung function are needed, since the published studies have methodological differences, mainly in the composition of the groups and in the time of the spirometric test.

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DIRECTIONS FOR FUTURE RESEARCH

- Study which other adverse conditions related to birth can influence lung function, not just weight.
- Consider studies that evaluated lung function using more accurate measurements such as body plethysmography and gas dilution.
- More longitudinal cohort studies should be performed to understand whether poor lung function in adolescence influences lifetime morbidity and mortality.

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