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Impact of Birth Weight and Smoking on Lung Function in Patients with Asthma, COPD, and Healthy Volunteers

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article

Abstract

Background. Birth weight (BW) is an important factor for determining the development of the respiratory system. The majority of research analyzed the impact of BW on lung function in youth. BW influence and smoking on lung function in adults with asthma and COPD is an interesting issue.

Objectives. The aim of the study was to investigate relationships between BW, smoking, and lung function in adult healthy individuals and diagnosed with asthma or COPD.

Material and Methods. Four hundred seventy-nine subjects were divided into 5 groups: 123 healthy non-smokers, 180 healthy smokers, 72 non-smoking asthmatics, 57 smoking asthmatics, and 47 COPD patients. Relationships between 4 BW quartiles and lung function was analyzed with respect to smoking.

Results. Impact analyzes of BW, smoking, and asthma on FVC% revealed that asthma is the only significant differentiating factor in this spirometric parameter ($p < 0.01$). FEV1% was significantly influenced by asthma and BW, and FEV1/FVC% was exclusively influenced by asthma. Spirometric parameters increased proportionally to particular BW quartiles in healthy non-smokers group; however optimal BW quartile predicting increase of parameters was 2751–3250 g. In asthma, BW quartile predicting the increase of spirometric parameters was 3251–3750 g, but BW quartile predicting decrease of FEV1/FVC% was 2751–3250 g. The comparison of results between COPD group and results from other 4 groups showed that values of all parameters in patients with COPD did not change proportionally to all quartiles of BW. In terms of FEV1/FVC%, the proportional increase of parameter in BW quartile 2751–3250 g was observed.

Conclusions. BW, as independent factor influences on spirometric parameters of healthy individuals, patients with asthma, COPD in a differentiated manner depending on quartile of BW rather than on simple linear increase of BW, regardless of smoking (*Adv Clin Exp Med* 2016, 25, 6, 1207–1213).

Key words: asthma, smoking, COPD, lung function, birth weight.

There are several different environmental and constitutional factors that occur during fetal life and childhood that can influence lung function and may contribute to lung disease in adulthood. Among the environmental factors, active and passive smoking by a pregnant mother, passive smoking by a new born child, malnutrition, respiratory tract infections, air pollution, and low social status have all well-known harmful effects on the

structural and functional lung development [1]. Among the constitutional factors, birth weight (BW) seems to play the major role in this regard, compared to the many pre- and perinatal indicators, for example pregnant detrimental conditions (mother's chronic diseases, addictions, intrauterine infections) and peri-obstetric damages caused by an incorrect fetus position as well as placenta or umbilical cord pathology [1–3].

Children with a low BW (LBW) are usually preterm born, and their respiratory system does not provide adequate gas exchange in their lungs, along with efficient oxygen and carbon dioxide distribution throughout the body [1]. In the later years of life in these children we often observe worse ventilation parameters than in their peers with a normal BW [2]. This particular group of children often suffers from both infant respiratory distress syndrome and bronchopulmonary dysplasia (BD), which may be risk factors of chronic lung disease, although certain data suggests that ventilating disorders in children with LBW may be present independently of bronchopulmonary dysplasia BD [3].

There are a few studies that have shown dependence between BW and asthma [4–6]. Seidman et al. [4] analyzed the impact of LBW on the occurrence of asthma symptoms in a large group of youth up to the age of 17 years old. For this study, information was gathered on BW and other demographic data from 20312 male subjects born in Jerusalem between January 1967 and December 1971 obtained from the Jerusalem Perinatal Study. The results showed that the analyzed group of persons with LBW (< 2500 g) had a significantly increased risk of developing asthma during their childhood compared with youth who had a greater BW, regardless of confounding effects of ethnical origin, social class, paternal education, maternal age, and birth order.

Steffensen et al. [5] examined a population of 4795 young adult males to find an association between BW and asthma. The prevalence of asthma in males with BW < 2501 g was higher than in males with a BW between 3001–3500 g. Their other findings indicated that fetal growth retardation rather than preterm delivery of male infants was the main risk factor for developing asthma. Another study, performed by Wjst et al. [6] on 2470 school children aged between 5–14 years, found that bronchial hyperresponsiveness was significantly increased in the examined group with LBW compared to normal term born children with correct BW ($p < 0.001$). Moreover, asthma was also more frequent in term born children with LBW.

Despite extensive research on many aspects of the relationships between pre- and perinatal factors and lung function, the data obtained is still inconsistent. However, there is little research which refers to the relationship between BW and lung function in adults. In addition, few of the available studies were concerned with the effect of a very low BW (< 1500 g) on the ventilatory function of the pulmonary system in the subsequent years of life [2, 3]. Such studies are, therefore, confounded by many pre- and perinatal life period disor-

ders, like premature birth and BD. Therefore, this current study was developed to show the relationships between either constitutional (mainly BW), environmental (mainly smoking), and lung function parameters in healthy individuals and patients with asthma and chronic obstructive pulmonary disease (COPD) who were middle-aged, i.e., 40–50 years old or older.

Material and Methods

Four hundred and seventy-nine individuals participated in this study; they were under the care of the Family Medicine Outpatient Clinic, which closely cooperated with the Department of Internal Medicine, Geriatrics and Allergy at Wrocław Medical University. The diagnosis of COPD patients at this institute was according to GOLD (Global Obstructive Lung Diseases) criteria, and the diagnosis of asthma patients was according to GINA (Global Initiative for Asthma) guidelines. Healthy volunteers were recruited from persons registered at the Family Medicine Outpatient Clinic during prophylactic examinations and were free from any health complaints and demonstrated normal physical and laboratory findings. The study project including the patient's consent was approved by the Ethic Committee of Wrocław Medical University – final decision KB 99/2007.

The 479 participants were divided into 5 groups: 123 healthy non-smokers (HNS), 180 healthy smokers (HS), 72 non-smoking asthmatics (AN), 57 smoking asthmatics (AS), and 47 COPD patients (CP). The mean age \pm standard deviation (SD) was 47.94 ± 15.8 years in the HNS group; 44.59 ± 12.83 years in the HS group; 48.86 ± 15.08 years in the AS group; 53.61 ± 19.59 years in the AN group; and in the CP group it was 59.30 ± 11.36 years. The mean BW (grams \pm SD) was 3282 ± 541 g in the HNS group; 3396 ± 618 g in the HS group; 3392 ± 491 g in the AS group; 3232 ± 429 g in the AN group; and 3365 ± 579 g in the CP group.

BW was divided into 4 categories (quartiles): 1) < 2750 g; 2) 2751–3250 g; 3) 3251–3750 g; and 4) > 3750 g. A lung function test was performed according to ATS/ERS guidelines [7], using a Spirobank G spirometer (Medical International Research USA, Inc. Waukesha). In the COPD group, spirometry was performed after the patient inhaled 200 μ g of salbutamol.

In the four quartile groups, we have taken into account the BW of the following spirometric parameters: FVC (forced vital capacity), FEV1 (forced expiratory volume in 1 s), PEF (peak expiratory flow), maximal midexpiratory flow 25–75% (MEF25-75), and maximal voluntary ventilation

(MVV). Their values were presented as a percentage of normal values. To evaluate bronchial obstruction, the Tiffeneau index (FEV1/FVC%) was used. All patients who were diagnosed with asthma and COPD were in a stable disease stage. Pack-years smoking index was calculated by dividing the number of cigarettes smoked per day by 20 and then multiplying it by the number of years during which the person had smoked.

Statistical dependence between BW and smoking, as well as lung function tests in healthy individuals and asthma patients, was evaluated by multivariate analysis of variance (MANOVA) with three variables. In CP group a MANOVA with two variables and a least significant difference test was done.

Results

There were no significant statistical differences among all of the examined groups for the mean value of BW ($p = 0.17$), height ($p = 0.15$) and current body weight ($p = 0.88$). Pack-years smoking index was highest in the CP group, and significantly higher in all asthma patients than in the HS group ($p = 0.04$) (Table 1). All groups included in this study were different in terms of their spirometric parameters, and in the COPD group the lowest values of these parameters were observed irrespective of BW.

Results obtained from the MANOVA evaluating BW influence; pack-years smoking index, and asthma influence on FVC% showed that only asthma is the factor significantly differentiating this spirometric parameter ($p < 0.01$). The mean values of FVC% were significantly higher in healthy sub-

jects than in asthmatic patients, with the important influence of BW on this spirometric parameter, although it reflected only a positive trend between asthma and BW ($p = 0.08$). In patients without asthma the FVC% mean value in the BW quartile > 3750 g was higher than in the BW quartile between 3250–3750 g, but in patients with asthma the best value of FVC% occurred in the BW quartile 3251–3750 g group (Fig. 1 and 2).

The findings of a three-way analysis of variance (ANOVA) which indicated the effect of BW, smoking, and current asthma on FEV1% showed that asthma ($p < 0.001$) and BW ($p < 0.016$) were the factors which significantly influenced this spirometric parameter (Fig. 3). FEV1% increased parallel to BW in subjects without asthma, but in asthmatic patients an increase of this spirometric parameter ceased in the group with the BW quar-

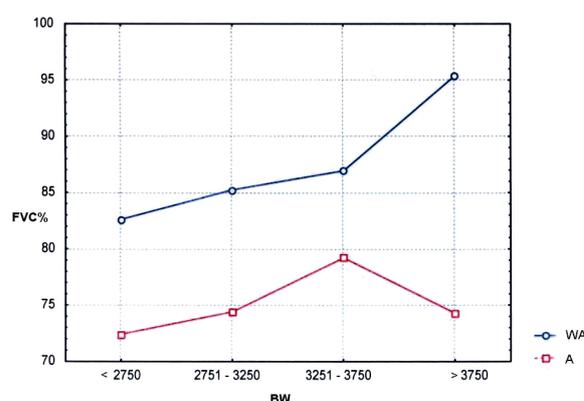


Fig. 1. Influence of asthma and BW on FVC% independently of smoking

A – asthma; BW – birth weight; FVC – forced vital capacity; WA – patients without asthma.

Table 1. General characteristics of the study population (mean ± SD)

Group	N	BW (g)	Age (years)	Height (cm)	Current weight (kg)	Pack-years smoking index
HNS	123	3282 ± 541	47.94 ± 15.87	167.1 ± 7.7	74.89 ± 16.95	N/A
HS	180	3396 ± 618	44.59 ± 12.83	168.6 ± 8.5	76.06 ± 17.70	16.4 ± 1.4
CP	47	3365 ± 579	59.30 ± 11.36	168.7 ± 7.6	73.80 ± 15.58	25.9 ± 1.6
AS	57	3392 ± 491	48.86 ± 15.08	167.3 ± 10.0	73.75 ± 16.61	21.0 ± 1.67
AN	72	3232 ± 429	53.61 ± 19.59	165.8 ± 10.1	75.08 ± 18.55	–
p-value*		p = 0.17	HNS : CP p < 0.001 HNS : AN p < 0.011 HS : CP p < 0.001 HS : AN p < 0.001 CP : AS p < 0.001 CP : AN p < 0.04	p = 0.15	p = 0.88	HNS : CP p < 0.001 HS : AS p < 0.038

*ANOVA – post-hoc test; AN – non-smoking asthmatics; ANOVA – analysis of variance; AS – smoking asthmatics; BW – birth weight; CP – COPD patients; HNS – healthy non-smokers; HS – healthy smokers; SD – standard deviation.

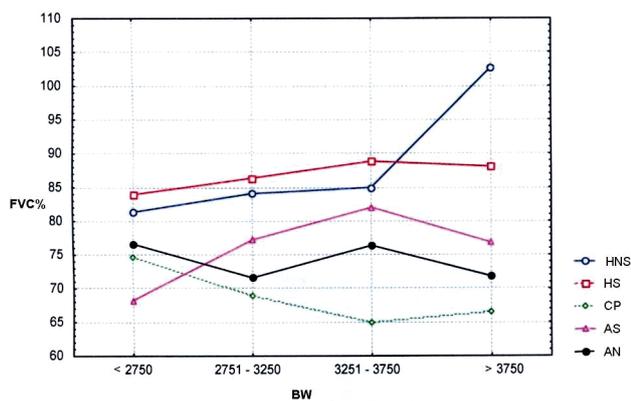


Fig. 2. Relationship between FVC% and BW in all study groups

BW – birth weight; HNS – healthy non-smoker; HS – healthy smokers; AN – non-smoking asthmatics; AS – smoking asthmatics; CP – COPD patients; FVC – forced vital capacity.

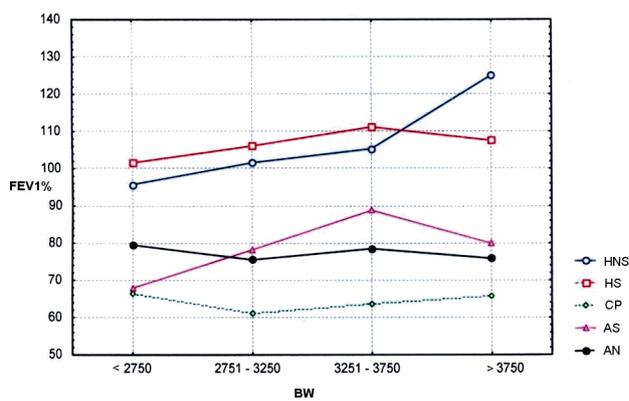


Fig. 4. Relationship between FEV₁% and BW in all study groups

BW – birth weight; HNS – healthy non-smokers; HS – healthy smokers; AN – non-smoking asthmatics; AS – smoking asthmatics; CP – COPD patients; FEV₁ – forced expiratory volume in 1 s.

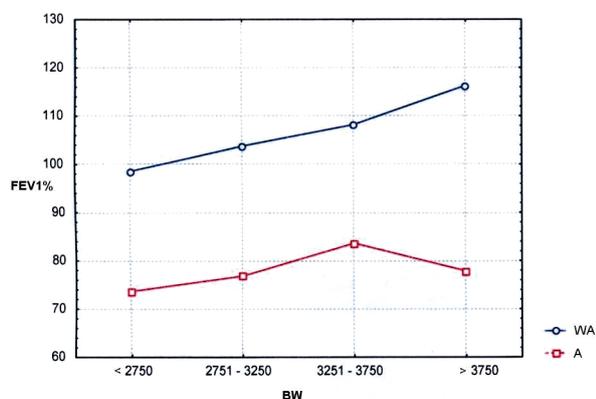


Fig. 3. Influence of asthma and BW on FEV₁%, independent of smoking

BW – birth weight; A – asthma; WA – patients without asthma; FEV₁ – forced expiratory volume in 1 s.

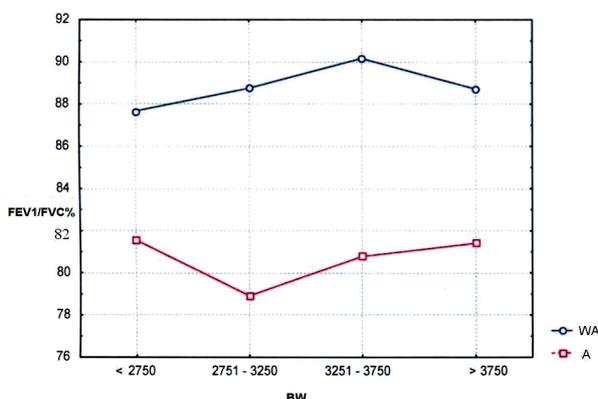


Fig. 5. Influence of asthma and BW on FEV₁/FVC%, independent of smoking

BW – birth weight; A – asthma; WA – patients without asthma; FEV₁/FVC % – forced vital capacity/forced expiratory volume in 1 s.

tile of > 3750 g. In the CP group the lowest values of FEV₁% were observed in all BW quartiles and there was no strong dependence between BW and the spirometric parameter in this group (Fig. 4).

Statistical data obtained by means of a three-way ANOVA concerning FEV₁/FVC% in the context of BW, smoking, and the presence of asthma showed that asthma was the only factor which significantly influenced this spirometric parameter ($p = 0.001$) (Fig. 5). FEV₁/FVC% increased in subjects without asthma together with BW up to a BW value of 3 750 g, and then decreased despite the high values of BW. The lowest values of FEV₁/FVC% were observed in the BW quartile 2751–3250 g, and in the CP group (Fig. 6).

Statistical ANOVA including BW, smoking, presence of asthma, and PEF% proved that asthma ($p < 0.001$) and BW ($p < 0.001$) significantly influenced this spirometric parameter. As in the pre-

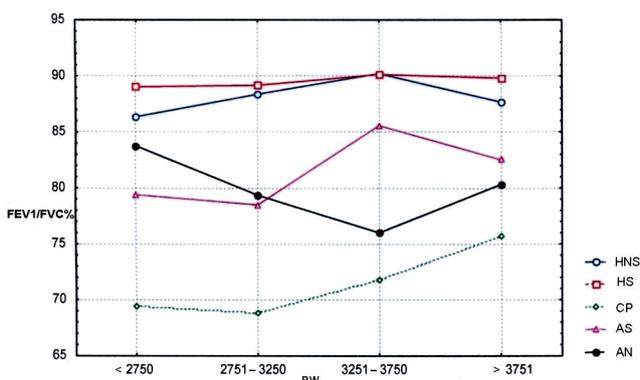


Fig. 6. Relationship between FEV₁/FVC % and BW in all study groups

BW – birth weight; HNS – healthy non-smokers; HS – healthy smokers; AN – non-smoking asthmatics; AS – smoking asthmatics; CP – COPD patients; FEV₁/FVC % – forced vital capacity/forced expiratory volume in 1 s.

vious analysis, PEF% increased parallel to BW in patients without asthma, with the exception of BW quartiles: 2750–3250 g and > 3750 g. PEF% had the lowest value in CP group except in the BW quartile < 2750 g.

A three-way ANOVA of the interactions between BW, smoking, presence of asthma, and MEF25–75% has indicated that asthma ($p = 0.001$) and BW ($p = 0.004$) significantly influenced this spirometric parameter. Further statistical calculation revealed a parallel increase in MEF25–75% to BW in patients without asthma, with the exception of BW quartiles: 2750–3250 g and > 3750 g. MEF25–75% values were the lowest in the CP group in all BW quartiles.

Asthma ($p = 0.001$) and BW ($p = 0.01$) were the factors which significantly influenced MVV% (three-way ANOVA) independently of the pack-years smoking index and reached its lowest values in the CP group (all weight quartiles), but in the HNS group MVV% values increased in the BW quartile > 3750 g.

A comparison of the results from the lung function tests in patients with COPD against those obtained in the other four groups generated by asthma and cigarette smoking has shown that values of FVC%, FEV1%, PEF%, MEF25–75%, and MVV% in patients with COPD did not change proportionally to any of the BW quartiles. However, with respect to FEV1/FVC%, proportional increase of this parameter in the BW quartile 2751–3250 g was observed (Fig. 6).

Discussion

Results obtained from this study indicate that the influence of BW on lung function parameters was different and might be a basis for open discussion with other published data. Generally speaking, BW is one of several factors which may affect lung function and could predict future lung development. Usually this issue has been analyzed in children [6] in terms of very LBW, which is connected with many pre- and perinatal disturbances [2, 3]. Our study was performed on a sufficiently large number of adult patients, and we attempted to demonstrate the influence of different BW quartiles on the most important spirometric parameters in this population. Furthermore, the influence of BW was analyzed in terms of chronic lung disease, such as asthma and COPD, and their reciprocal interaction with lung function.

Outcomes of the three-way ANOVA relating to the impact of BW, smoking and present asthma on FVC% showed that asthma was the only factor which significantly differentiates within this

parameter, and that this was also dependent on the BW quartile. This phenomenon was also observed in persons who had no asthma, nor any other chronic diseases. In the CP group FVC% was significantly lower among all BW quartiles, with the exception of the BW quartile < 2750 g, in which the lowest FVC% was observed in the AS group. However, in the categories of higher BW, higher values of FCV% were revealed in the AS group than in the CP group, which was further confirmed by the ANOVA outcomes. To date, little research has evaluated the relationship between BW and COPD. Inter alia, Hyde et al. [8] showed that in a group of preterm born children who had a LBW and BD, a higher prevalence of COPD was observed. Other studies displayed the frequent co-existence of emphysema with LBW [9, 10]. Independent of smoking influence on asthma, the FVC% levels observed in this study was also confirmed in previous studies [11, 12].

Furthermore, we demonstrated that in relation to BW, smoking and asthma, only asthma and BW had a significant influence on FEV1%. Peat et al. [13] compared the FEV1% values in 2 groups, 92 subjects with asthma and 186 healthy subjects, and showed that FEV1% decreased in the asthmatic subjects by 50 mL/year compared with 35 mL/year in the healthy subjects. Kupczyk et al. [14] observed the correlation between lung function decline, age, gender, and asthma in a large cohort group study, with the reduction of FEV1% shown to be very fast (80 mL/year). In our study, FEV1% increased parallel with BW in subjects without asthma, but in asthmatic patients the increase of this spirometric parameter ceased in the BW quartile > 3750 g group. A similar observation was found by Bakke [15], who noticed that a negative effect of atopy and bronchial hyperresponsiveness – a pivotal feature of asthma – lead to a decrease of FEV1%.

FEV1/FVC% is an essentially important parameter in the diagnostic process of airway obstruction and COPD. Our study showed that asthma was the only factor which significantly influenced this spirometric parameter, and in asthmatic patients the lowest values were in the BW quartile 2751–3250 g group. Moreover, this spirometric parameter was lower in the AS group than in the AN group, but only in the BW quartiles < 2750 g and 2751–3250 g. In the other BW quartiles FEV1/FVC% was higher in AS than in the AN group, which indicates the important role of BW, regardless of smoking in this relationship. In the HS group, FEV1/FVC% was significantly higher than in the AS group which points to the dominant influence of asthma on this spirometric parameter. Results obtained from previ-

ous studies appear to be consistent with our findings [13, 14].

In this study, statistical analysis showed that the factors significantly influencing PEF% were asthma and BW, independent of smoking, and that the highest PEF% values in asthmatic patients were observed in the BW quartile 3251–3750 g group. In subjects without asthma, PEF% increased gradually and reached its highest values in the BW quartile > 3750 g group. Similar results were obtained by Lodrup et al. [16], who measured lung function parameters in 803 healthy infants with a mean BW of 3590 g.; however, authors found that the PEF% values increased parallel with BW. In our study some very interesting observations arose from the analysis of PEF% values amongst the various BW quartile groups. The most reliable comparative data related to the BW quartile > 3750 g group, in which PEF% had the highest value in the HNS group and was significantly different in comparison with all other groups.

The next lung function parameter to be taken into account in our study was MEF25-75%, which is the most reliable indicator in the spirometric parameter group that expressed airway obstruction in the middle period of expiration (MEF25%, MEF50%, and MEF75%) [17]. Interpretation of the changes in these parameters (including MEF25–75%) is very difficult due to their low diagnostic specificity and variability in the healthy population [18]. Furthermore, it is advisable to interpret MEF25-75% together with other spirometric parameters, e.g., FVC, FEV1, and PEF [19]. In our study, statistical analysis of the interactions between BW, smoking, asthma, and MEF25-75% revealed that asthma and BW significantly influenced this spirometric parameter. Additionally, MEF25-75% increased gradually in the group without asthma, but in patients with asthma it remained nearly at the same level, with the exception of the BW quartile 3251–3750 g group. Previously published data suggests that in asthma the values of this parameter seem to depend on the activity of the inflammatory process in the bronchial tree [20].

The last parameter analyzed in this study was MVV%. This parameter reflects respiratory muscle strength, lung and thorax compliance, and airway resistance [17]. An ANOVA showed 2 factors which significantly influenced MVV% – asthma and BW. The most significant differences connected with this spirometric parameter were observed in the group with a high BW. In the BW quartile > 3750 g, MVV% was highest in the HNS group compared to any other group. CP had a significantly lower MVV% than in any other group, with one exception in the AN group. This unexpected observation may be caused by an increase of airway resistance during hyperventilation, which is a well-known phenomenon in asthma; hence, we should evaluate the probability of asthma and BW influence on this spirometric parameter with caution. The general trend of MVV% increasing in the HNS group, together with BW increasing (especially in the BW > 3750 g group), may have been caused by a higher tolerance of physical exertion in this group of people. Relationship between MVV and exercise capacity is observed not only in healthy non-smoking persons. According to the data published by Ong and Wang [21], there is a connection between MVV% and other parameters of lung function especially FEV1/FVC ratio and FEV1, with an increase of tolerance for physical exertion in patients with COPD.

Outcomes of this study clearly suggest that BW in a differentiated not linear manner but depending on the BW quartiles, i.e., scope of BW category influence the spirometric parameters as an independent factor, mainly in patients suffering from asthma and COPD. In healthy subjects the influence of BW on lung function is proportional to the BW range, independent from smoking. The BW category range, which best predicts the values of spirometric parameters in asthma, is the BW quartile 3251–3750 g. Asthma itself is an independent factor influencing the values of such indices of lung function such as FVC%, FEV1%, PEF%, MEF25–75%, FEV1/FVC%, and MVV%. In COPD patients, FEV1/FVC% is the parameter that is connected with BW.

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