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ORIGINAL ARTICLE

ASSOCIATION BETWEEN RESPIRATORY FUNCTION AND BONE MINERAL DENSITY IN PUBERTAL AND PREPUBERTAL HEALTHY CHILDREN

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Abstract:

Aim: *We aimed to evaluate whether the variation in bone mineral density (BMD) measures correlates with the respiratory function parameters and to determine the association between lung function tests and anthropometric indices in healthy pubertal and prepubertal children.*

Methods: *We recruited 73 school children. Primary school students were representing prepubertal children and high school students were representing pubertal children. Data collection included a questionnaire and measures of anthropometry, respiratory function and BMD. We investigated the associations between BMD with spirometric parameters and anthropometry with spirometric parameters controlling for pubertal status and other relevant variables.*

Results: *We studied 73 school children (36 prepubertal and 37 pubertal; mean age=12.47±4.26 years). Mean BMD z-score values were significantly different between FEV1 percent predicted quartiles which showed a tendency to increase with the trend in FEV1 percent predicted quartiles. In addition, there was a significant correlation between BMD SOS values and PEF percent predicted values. However, in models controlling for possible confounders, this association of BMD SOS with PEF percent predicted values vanished. When controlled for puberty, FVC percent predicted values were positively associated with BMI SDS (r=0.35, p=0,004) and MAC (r=0.29, p=0.018) and FEV1/FVC percent predicted values were negatively correlated with BMI SDS (r=-0.40, p=0.001) and MAC (r=-0.485, p<0.001). The FEV1/FVC percent predicted values were significantly lower in the overweight group than in non-overweight group.*

Conclusion: *Although the measures of BMD correlate with respiratory function parameters, this association is likely to arise from common influential factor or factors, rather than being a cause-effect relationship.*

Keywords: *: respiratory function, bone mineral density, healthy children*

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INTRODUCTION

Bone mineralization is a complex process that requires adequate nutrition, protein for osteoid formation, calcium and phosphorous for calcification, weight-bearing and muscle use, and modulation by thyroid, parathyroid, gonadal, and pituitary hormones and other growth factors (1,2). From infancy through late adolescence, the activity of bone formation predominates, resulting in a steady accumulation of bone mass (3,4). Puberty has a key role in bone development and skeletal mass approximately doubles at the end of adolescence (3). Meanwhile, body weight and height are also two of the important factors affecting BMD (5,6).

Bone mineral density (BMD) and fragility fractures in adults have been associated with numerous genetic, nutritional and environmental factors (7,8). In clinical

studies, in patients with respiratory diseases such as cystic fibrosis and bronchial asthma, measures of respiratory function have correlated with bone mineral density (9,10). It should be noted that in addition to compromised lung function, patients with these conditions are exposed to a variety of other factors that might impair their bone health. For example, cystic fibrosis is associated with pancreatic malabsorption and bronchial asthma is often treated with long-term corticosteroids. Only a few studies have evaluated the relationship between respiratory function and BMD in healthy populations, and they have been restricted to certain age groups (11,12). Therefore it is not clear whether the observed association between respiratory function and BMD simply is restricted to patients with chronic respiratory diseases or whether it applies to all age groups.

In the present study, we aimed to investigate whether variations in respiratory function has an influence on bone mineral density in healthy children. As a secondary outcome, variations in lung function accross the range of anthropometric parameters and the role of obesity on respiratory function was assessed.

MATERIALS AND METHODS

This cross-sectional study was done in a primary school and a high school in Istanbul. Thirty-six children attending primary school in the 2nd and 3rd grades and 37 children attending high school in the 2nd grade were studied. Primary school students were representing prepubertal children and high school students represented pubertal children. In order to exclude the probability that some of the children might have entered puberty, pubertal stages (13) of the primary school children were assessed. Pubertal stage assignment was made according to breast development in girls and pubic hair development in boys. A consent form was signed by all parents before participation in the study. The study protocol was approved by the ethics committee of the Medical Faculty of Yeditepe University. Consent was obtained from parents of all children. A questionnaire was filled out by the parents for the primary school children and the high school students filled out the questionnaire themselves. Information regarding demographic properties, exposure to cigarette smoke, family history of atopy, performance of regular sportive activities, consumption of carbonated beverages and past medical history of lung infection were collected from the study group. Children with a history of asthma, an atopic disease or a chronic disease were excluded from the study. Dairy product consumption in three-day diets were recorded and dietary calcium intake was calculated for all children using USDA National Nutrient Database (14). An adequate dietary calcium intake was defined as ≥800mg and ≥1300mg for prepubertal and pubertal children, respectively (15).

Collection of anthropometric data

Measurements of weight, height, thickness of the triceps skin folds (TSF), mid-upper arm circumference (MAC) were performed using standardized methods. Standard deviation scores (SDS) and percentile values of body mass index (BMI) and height for age were calculated for each child by reference to the National Center for Health Statistics (NCHS) Standard values (16). BMI was calculated as weight per height^2. Weight was measured in kilograms with an electronic device with 100 g intervals. Height was measured with 1 mm intervals by a standard stadiometer in centimeter (cm). Measurements of triceps skin fold were done with a Holtain caliper (0.1 mm intervals) at the midpoint of the acromion-olecranon of the extended left arm. Mid-upper arm circumference was measured at this point. BMI (weight/height^2) >95th percentile according to age and sex was accepted as obesity and >85th percentile was defined as overweight.

Quantitative Bone Ultrasound

Quantitative ultrasound (QUS) is a relatively new modality for assessment of bone. The United States Food and Drug Administration has recently approved the use of some QUS devices for the routine diagnosis of bone mineral status and determination of fracture risk (17). It has the advantage of being radiation-free, noninvasive, mobile and friendly to both user and patient, making it ideal for use in children. Studies using QUS have found varying but generally good correlation with dual-energy x-ray absorptiometry (DXA), and QUS technique has been shown to be a good predictor of fracture risk in postmenopausal women, independent of D-XA (18). We evaluated bone status in children with quantitative ultrasound. Quantitative Bone Ultrasound Measurements of the velocity of ultrasound wave, expressed as speed of sound (SOS) in m/s, were performed using the Omnisesnse 7000P, ultrasound bone sonometer device (Sunlight Ltd., Tel Aviv, Israel) at radius. The examination site corresponded to the point halfway between the edge of the olecranon and the tip of the distal phalanx of the outstretched third digit of the left hand. A specialized pediatric transducer was placed on the marked site of measurement and rotated without lifting the transducer from the skin. SOS measurements were repeatedly performed. When the SOS score was reproducible three times in a row at the premarked location, that measurement was used. The measurements were analyzed by Pediatric Version 2.0.1 copyright © 2002 software. Z-scores (difference between the patient's value and the agespecific mean value divided by the reference group's Standard deviation) were calculated in all patients. The reference group was represented by more than 1000 healthy Israeli children and adults (database gathered by Sunlight Company) (19). The non-dominant side was uniformly used for examinations; this was usually the left side unless a history of fracture was present. The device was calibrated before each examination against a control block

supplied by the manufacturer. For 61 children BMD measurements were obtained.

Spirometric Measurements

Respiratory function parameters were measured with a Clement Clarke 2002 SN CE0120 (UK) spirometry device in accordance with the recommendations of the European Respiratory Society, at room temperature by the same investigator (20). Before each measurement the spirometer was calibrated. Subjects were made to rest for 15 minutes before measurements and were informed about the procedure. After the appropriate placement of the mouthpiece and nose click, a powerful, quick, forced expiration challenge was done just after maximum forced inhalation. By doing at least three technically appropriate measurements, the highest value was recorded as basal value. Forced vital capacity (FVC) (L), forced expiratory volume in one second (FEV1) (L), FEV1/FVC (%), peak expiratory flow (PEF) (L/min) were measured with spirometry. All these parameters were represented as percent of Polgar reference values, which were designated according to age, sex, weight and height (21).

Possible Confounding or Mediating Variables

We assessed the relationship between BMD parameters and spirometric parameters controlling for: (1) age (or pubertal status), (2) gender, (3) physical activity, (4) anthropometric measurements, (5) dietary calcium intake and (6) excessive consumption of carbonated beverages.

Statistical analysis

The associations between BMD parameters (SOS and SOS z-score) and spirometric parameters were initially investigated by bivariate statistical models. The children were divided into quartiles according to FEV1 percent predicted values. Radius SOS values and SOS z-score values were compared among these groups by using One-Way ANOVA test. The correlations between spirometric measurements with BMD parameters and anthropometric indices were assessed by Pearson correlation coefficients. Spirometric measurements of overweight and non-overweight children were compared by Student's t-test. Then we investigated the relationship between BMD and spirometric parameters simultaneously with other relevant variables that might affect the investigated parameters such as age (or pubertal status), gender, physical activity, dietary calcim intake, consumption of carbonated beverages and anthropometric parameters by multivariate models. To investigate the relationship between respiratory function and anthropometry, a linear regression model was fitted with spirometric data as the dependent variable and anthropometric parameters as independent variables with and without other covariates in the model. The results were expressed as number and percentage or mean ± standart deviation. A p-value less than 0.05 was considered as significant. SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

RESULTS

We studied 73 school children with an age of 12.47±4.26 years (min=7.2 years, max=18.34 years). Thirty-six of them were in the 2nd and 3rd grades in primary school and 37 of them were in 2nd grade in high school. The primary school students were prepubertal children and the secondary school students represented pubertal children. The anthropometric indices, BMD parameters and spirometric parameters are presented in Table 1. The prevalences of obesity and overweight were 24.7% and 45.2%, respectively.

The correlations between BMD parameters and spirometric measurements

Mean Speed of sound z-score values were significantly different between FEV1 percent predicted quartiles ($p=0.03$). Mean (and SD) SOS z-score values in FEV1 quartiles are shown in Table 2. Although SOS z-scores increased parallel to the FEV1 percent predicted quartiles except for the lowest quartile, the post hoc Tukey HSD test indicated the significant difference only between second and fourth quartiles ($p=0.029$).

When analysing the correlation between spirometric measurements and radius SOS values, we found that there was a significant correlation between radius SOS values and PEF percent predicted values ($r=-0.34$, $p=0.009$), but not with other spirometric measurements. It should be noted that there was also a significant correlation between age and PEF percent predicted values as well as age and radius SOS values. However, when we adjusted for age, the association between radius SOS and PEF percent predicted values became insignificant. Finally, the multivariate model for radius SOS analyzed the effects of PEF, pubertal status, gender, physical activity and dietary calcium intake. In this model, dietary calcium intake, physical activity and puberty were the significant explanatory variables, but PEF percent predicted value was not a significant explanatory variable.

B. The correlations between anthropometric parameters and spirometric measurements

When we compared the spirometric parameters of the overweight group with those of non-overweight children we found that FEV1/FVC percent predicted values were significantly lower in the overweight group (Figure 1). FEV1/FVC percent predicted values were 95±20 and 105±10 for the overweight and non-overweight children, respectively ($p<0.0001$). Other spirometric measurements were not significantly different between the two groups.

Table 1: Anthropometric and spirometric measurements and bone quantitative ultrasound parameters of study group.

	Primary school grades 2 and 3 students (n=36) Mean±SD		High school 2nd grade students (n=37) Mean±SD		Significance and power
Age (years)	8.22 ±	0.55	16.61 ±	0.71	t=13.91 p<0.001 Power=100%
BMI SDS	1.34 ±	1.21	0.83 ±	1.15	t=1.84 p=0.069 Power=45%
HFA SDS	0.59±	0.87	-0.03±	0.86	t=3.07 p<0.05 Power=90%
MAC (cm)	21.9 ±	3.8	27.4 ±	4.2	t=-5.82 p< 0.001 Power=100%
TSF (mm)	16.45 ±	5.58	18.61 ±	12.6	t=-0.93 p=0.35 Power=15%
FEV1/FVC (%)	86.16 ±	7.84	87.08 ±	7.91	t=-0.49 p=0.63 Power=8%
FEV1/FVC percent predicted	100±	8.7	101±	9.6	t=-0.48 p=0.62 Power=5%
PEF (L/s)	212.6 ±	62.04	437.2 ±	89.7	t=-12.24 p<0.001Power=100%
PEF percent predicted	85±	16.9	102±	17.4	t=-4.75 p<0.001 Power=100%
FEV1(L)	1.77 ±	0.44	3.78 ±	0.85	t=-12.49 p<0.001 Power=100%
FEV1 percent predicted	101±	14.6	112±	14.7	t=-3.76 p<0.001 Power=99%
FVC (L)	2.05 ±	0.55	4.38 ±	1.11	t=-11.07 p<0.001 Power=100%
FVC percent predicted (%)	101±	14.9	108±	14.6	t=-2.51 p=0.01 Power=99%
Radius SOS values (m/sec)	3626 ±	162	3919 ±	137	t=-7.41 p<0.001 Power=100%
SOS z-score	-1.0±	1.08	0.08 ±	0.96	t=-4.63 p<0.001 Power=100%

BMI SDS: Body mass index standard deviation scores, HFA SDS: Height for age standard deviation scores, MAC: Mid-upper arm circumference, TSF: Triceps skin fold thickness, FVC: Forced vital capacity. FEV1: Forced expiratory volume in 1 second. PEF: Peak expiratory flow. SOS: speed of sound. SOS and SOS z-score values were obtained from 61 children.

Table 2: Mean radius SOS z-score values in FEV1 percent predicted quartiles in study group.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Mean SOS (±SD) z-scores	-0.68(0.29)	-1.48(0.42)	-0.24(0.27)	-0.09(0.27)

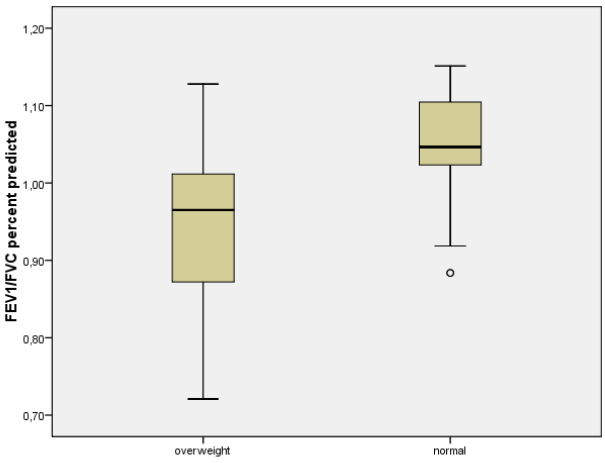

Figure 1: FEV1/FVC percent predicted values of overweight and normal children.

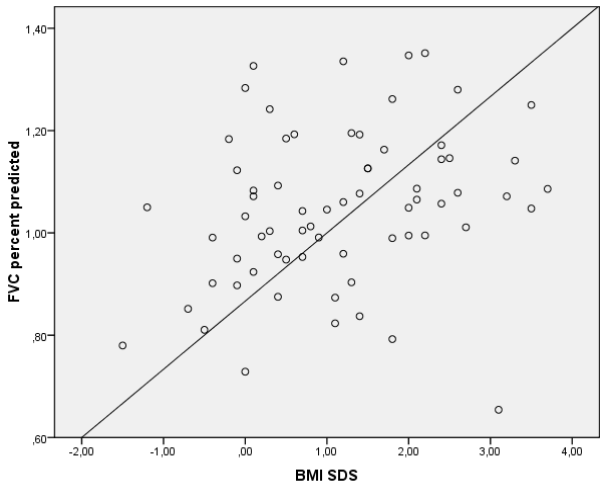

Figure 2: FVC percent predicted values and BMI SDS.

When we analyzed the correlation between anthropometric measurements and spirometric parameters; there was a significant correlation between height for age SDS and PEF percent predicted values. There was a significant positive correlation between body mass index SDS and FVC percent predicted values (r=0.26, p=0.03) and negative correlation between body mass index SDS and FEV1/FVC percent predicted values (r=-0.41, p<0.0001). Mid upper arm circumference was also negatively correlated with FEV1/FVC percent predicted value (r=-0.33, p=0.005), and positively correlated with PEF percent predicted value (r=0.29, p=0.013), and FVC percent predicted values (r=0.37, p=0.002). Triceps skinfold thickness was not significantly correlated with any of the spirometric parameters.

In the second step, to eliminate the confounding effect of age and puberty, we analyzed these associations controlling for age and pubertal status. In the multivariate analyses, the FVC percent predicted values were positively associated with the body mass index SDS (r=0.35, p=0,004) (Figure 2) and mid upper arm circumference values (r=0.29, p=0,018). The FEV1/FVC percent predicted values were negatively correlated with the body mass index SDS (r=-0.40, p=0.001) and mid upper arm circumference (r=-0.485, p<0.001). The associations between the PEF percent predicted values and anthropometric parameters became insignificant when controlled for age.

DISCUSSION

We observed that mean radius SOS z-score values have a tendency to increase with the trend in FEV1 percent predicted quartiles. In addition, there was a significant correlation between radius SOS values and PEF percent predicted values. However, in models controlling for possible confounders which might independently affect BMD, such as gender, dietary calcium intake, anthropometry, physical activity and puberty, this association of radius SOS with PEF percent predicted values vanished. These findings imply that the association of BMD measures and respiratory function is not a simple cause–effect relation, but rather is likely to reflect the role of some common factors that independently influence both parameters.

Bone mineral density (BMD) is the best predictor available for fracture risk, accounting for more than 60% of the variance in breaking strength, although it is influenced by numerous genetic, nutritional and environmental factors (22,23). Various systemic disorders such as vitamin D deficiencies, type 1 diabetes mellitus, osteogenesis imperfecta, untreated long-standing hyperthyroidism, hypogonadism, chronic malnutrition, malabsorption (especially coeliac disease), chronic liver disease and Cushing's disease as well as chronic obstructive lung diseases are associated with osteoporosis. It has been shown that as many as 60% of adult patients with obstructive airways disease have osteoporosis (24). An analysis of the Third National Health and Nutrition Examination Survey (NHANES) revealed that the risk of osteoporosis among males and females was inversely correlated with the degree of their airway obstruction (25). Adjustment for age, smoking, BMI, physical activity and different types of medication (among others, inhaled or oral corticosteroids, bronchodilators and oestrogens) did not change these results. On the other hand, in a study evaluating the bone mineral density of children with non-cystic fibrosis bronchiectasis, rather than the severity of lung illness, the age of the subjects was found to be associated with osteoporosis and osteopenia (26).

In a Japanese study involving elderly female subjects with COPD who had not been exposed to oral corticosteroids, the prevalence of osteoporosis was 50%, twice as high as a comparison group consisting of females of the same age with asthma (27). Similarly several pediatric studies have

demonstrated that whole body bone mineral content is decreased in children and adolescents with cystic fibrosis (28-31). In a recent study, it was shown that in approximately one-third of pediatric patients with cystic fibrosis, bone mass was lower than expected for chronological age (32). Several mechanisms have been suggested for this possible relationship between OAD and increased risk of fracture or osteoporosis, including lack of physical activity (33,34), low BMI among patients with COPD (35), smoking (36), a decreased exposure to sunlight (26), decreased testosterone levels (37), hypercapnia (38), and chronic inflammation. These findings indicate that normal respiratory function is one of the factors required for the maintainance of healthy bone mineralization.

Lekamwasam et al. (12) examined the relationship between bone mineral density and respiratory function in women from the general community and reported that there was a positive and continuous relationship between FEV1 and bone mineral density at the hip across the whole normal range of respiratory function. Later on, the researchers reproduced the same findings in older men with the association being weaker than in women (12,13). Although, use of inhaled corticosteroids was not evaluated, the results remained similar after exclusion of patients who had a history of respiratory disease (12). They concluded that poor respiratory function may be a useful indicator of women at increased risk of osteoporosis. The age group of their study population represents a life stage in which individuals are at an increased risk for osteoporosis. Therefore, it could be expected that even minor alterations in factors that play roles in bone health might be easily translated into the measures of BMD at this age group. In contrast, our study group represents an age interval at which a great amount of bone mineral content is achieved. In this age group, subjects are generally physically active and hormonal changes promote bone mineralization so that osteoporosis is an unusual condition unless the subjects suffer from chronic diseases that might affect BMD. Therefore, even if respiratory function is one of the factors influencing BMD, in the absence of major alterations in lung function, this association could be hardly detected in this age group. A potential drawback to our study might be the measurement of BMD by quantitative US technique. Larger studies with DXA, the gold standard method for bone density assessment, would elucidate the exact influence of respiratory function on bone density in children.

Striking changes in body composition occur during puberty, along with an increase in gonadal hormone levels (39). Prepubertal boys and girls start with equal lean body mass, skeletal mass, and body fat, but during pubertal development, boys accumulate more skeletal and lean body mass than girls, who accumulate more fat mass than boys. By maturity, men have 1.5 times the lean body mass and almost 1.5 times the skeletal mass of women, whereas women have twice as much body fat as men (40,41). Previous studies have shown that the main increase in BMD occurs during puberty with an increase in the concentration of growth hormone and sex steroids, which are known to have a positive influence on bone mineralization (42,43). In addition, it was shown that body weight and height are two of the important factors that affect BMD (5,6). Puberty is also a time of significant weight gain (44). Therefore, we included both prepubertal and postpubertal children in our study to eliminate the confounding effects of conditions related with the pubertal developmental process. Presumably, there is a complex interaction between hormonal factors, anthropometry, BMD, respiratory function, physical activity and nutrition. Therefore, it is possible that the correlation between BMD measures and respiratory function parameters might reflect the shared influence of other factors such as sex steroids and body composition, which show great variations along with puberty.

Several studies have demonstrated an association between obesity and pulmonary dysfunction and the most frequent alterations in the respiratory function parameters of obese children were reported to be reduction of lung volumes and the diffusion capacity of carbon monoxide (45). In a pediatric study, Ulger et al. (46) evaluated the effect of obesity on respiratory function and demonstrated that although there were no asthma symptoms, airway hyperresponsiveness was positive in 18.4% of the obese subjects, and this was statistically higher than in the control group. Thomas et al. (47) reported that after weight loss, significant increases might be detected in FRC, residual volume, total lung capacity, and expiratory reserve volume. Inselma et al. (48) reported that obese children have altered pulmonary function, which is characterized by reductions in lung diffusion capacity, ventilatory muscle endurance and airway narrowing. It was suggested that these alterations might reflect extrinsic mechanical compression on the lung and thorax, and/or intrinsic changes within the lung and the reduced diffusion capacity might result from decrease in alveolar surface area relative to lung volume.

In the Ulger et al. study, basal respiratory function test parameters were lower in the obese group as compared with the control group and there were strong negative correlations between BMI, relative weight, skin fold thickness, waist/hip circumference ratio and basal FVC, FEV1, and PEF values (46). In the Lazarus et al. study (49), adjusted FVC and FEV1 values in children decreased significantly with increasing total body fat percent. Within each age and gender group, ventilatory function decreased with the increasing proportion of body fat. In a study done by Zerah et al. (50), expiratory flows diminished in proportion to lung volumes, and the FEV1/FVC ratio was within normal limits in obese patients. In the Ulger et al. study (46), the FEV1/FVC ratios of the study and control groups were also similar. They concluded that both respiratory resistance and airway resistance rise significantly with the level of obesity, suggesting that in

addition to the elastic load, obese subjects have to overcome increased respiratory resistance resulting from the reduction in lung volumes related to being overweight.

When we analyzed the correlation between anthropometric measurements and spirometric parameters, there was a significant correlation between the PEF percent predicted values and HFA SDS and MAC. BMI SDS and MAC were positively correlated with the FVC percent predicted values and negatively correlated with the FEV1/FVC percent predicted values. Muscle mass is a nutritionally important compartment because it is the most variable component of lean soft tissue mass. Arm measures such as MAC are meant to function as indexes of total muscle mass. Because the relation between subcutaneous fat and deep fat, and hence between skinfold-thickness measures and fat mass or percentage body fat, varies depending on age, sex, and maturity, we evaluated the relationship between anthropometric indices and pulmonary function tests controlling for pubertal status. When adjusted for pubertal status and age, the FVC percent predicted values were positively associated with BMI SDS (R=0.35, P=0.004) and the MAC values (R=0.29, P=0.018), but the FEV1 values did not have a significant correlation with anthropometric indices. The FEV1/FVC percent predicted values were significantly lower in the overweight group compared to the children with normal BMI SDS values. Other spirometric measurements were not significantly different between the two groups. These findings imply that across the normal range of BMI, lung volume is mainly determined by the body fat mass and muscle mass of the subject; however, in overweight children there is a reduction in ratio of flow rate over lung volume, indicating a tendency for obstructive airway disease.

In conclusion, in a sample of healthy children, although measures of BMD were found to correlate with respiratory function, this association is likely to arise from common influential factor or factors, rather than being a cause-effect relationship. It is possible that hormonal changes associated with puberty mediate these interactions. Whereas FVC relates with the surrogate markers of body fat mass and muscle mass in children across the whole normal range of BMI, obesity is associated with a decrese in FEV1/FVC ratio. Larger studies including children at different stages of pubertal development could identify the precise role of respiratory function on bone density.

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