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Weight Status and Respiratory Health in Asthmatic Children

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Abstract

In this study,we explored the effect of adiposity as measured by BMI on lung function in 72 asthmatic school children (5–12 years) using baseline data from the Mediterranean diet enriched with fatty fish intervention study. Bronchial function was assessed using spirometry and fractional exhaled nitric oxide (FeNO). BMI categories were classified as normal and overweight/obese based on International Obesity Task Force cut-offs. Weak correlations were observed between BMI and FVC ($p = 0.013$) and FEV_1 ($p = 0.026$). Median FeNO was lower in the overweight/obese as compared to normal weight group ($p = 0.027$). Linear regression showed an increment in $FEF_{25–75\%}$ in the overweight/obese group as compared to normal weight after controlling for confounders namely age, height, sex, regular physical activity, medication and KIDMED score ($p = 0.043$; $\beta = 11.65$ units, 95% CI 0.36–22.94), although with no effect on FeNO. In conclusion, the findings of this study suggest that excess body weight could impact pulmonary dynamics in childhood asthma.

Keywords Asthma · Body mass index · Children · Lung function · Spirometry · Overweight

Abbreviations

BMI	Body mass index
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
FEV_1/FVC	Ratio of forced expiratory volume in 1 s and forced vital capacity
PEF	Peak expiratory flow
$FEF_{25–75\%}$	Mid expiratory flow 25–75% vital capacity
FeNO	Fractional exhaled nitric oxide

Introduction

The universal rise in paediatric asthma and obesity are two chronic conditions that warrant urgent attention in public health [1]. Both conditions are associated with adverse effects on lung function and contribute to increased morbidity and disability during childhood [1]. There is compelling epidemiological evidence supporting an association between obesity and asthma prevalence/severity in children suggesting a common pathophysiology between these two conditions [1]. Nevertheless, there is limited understanding of the effect of adiposity on pulmonary function in paediatric patients with mild asthma. Previous research has shown that 70% of asthmatic patients suffer from 'mild asthma' [2]. Mild asthma is more frequent, more symptomatic, and less well controlled in children than in adults

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[2]. Severe exacerbations in mild asthma represent 30–40% of asthma exacerbations requiring emergency consultation [2]. Our recent work on the Mediterranean diet and asthma revealed that increased fatty fish intake reduced bronchial inflammation in asthmatic children [3]. Using baseline data from this dietary intervention study, we opted to explore the effect of adiposity as measured by Body Mass Index (weight/height^2) on lung function in Greek asthmatic school children.

Methods

The present study was a cross-sectional analysis of the Mediterranean diet enriched with fatty fish and paediatric asthma intervention study. The sampling procedure took place from November 1st to December 31st, 2016. The design and study protocol have been described in detail in Online Resource 1. In brief, after signed informed consent, 72 children aged 5–12 years, with physician-diagnosed mild asthma [4] were recruited from a private paediatric asthma clinic in the greater city of Athens, Greece. The primary outcomes were pulmonary function indices (FEV_1, FVC, FEV_1/FVC, PEF, $FEF_{25–75\%}$), reported as percent predicted values of pre-bronchodilator administration and bronchial inflammation biomarker, fractional exhaled nitric oxide (FeNO). In this manuscript the primary exposure of interest is BMI [5]. Pulmonary function tests were performed by trained personnel following standard protocol [6] using a portable spirometer MIR Spirobank II (MIR Inc. USA) and eosinophilic airway inflammation by a portable FeNO analyser (NO breath, Benfont Inc.UK) [7]. Normal pulmonary function in children was defined as FEV_1, FVC, FEV_1/FVC, PEF $\geq$ 80% predicted, and $FEF_{25–75\%} > 60–65\%$ [8]. A threshold of 20 ppb was used as cut-off to define eosinophilic inflammation in children [9]. Body weight and height were assessed using calibrated electronic scales and stadiometer (SECA, Hanover, MD) followed by BMI calculation. BMI categories were classified either as normal, overweight or obese as stated by the International Obesity Task Force (IOTF) cut-offs [5]. All procedures performed in this study were in accordance with the ethical standards of the institution (La Trobe University Human Ethics Committee, HEC 16-035) and with the 1964 Helsinki declaration.

Statistical Analysis

Continuous variables were assessed for normality using graphical methods and Shapiro–Wilks test. Given that only seven subjects were obese, data for overweight and obese were combined and BMI was stratified to two groups, normal weight versus overweight/obese. Differences between groups were compared using independent *t* test, Mann–Whitney test for skewed variables and Chi Square Test for frequencies. Spearman's correlation and linear regression were fitted to estimate the association between BMI and lung function parameters and FeNO. Potential confounders namely age, sex, height, regular physical activity ($\geq$ 3 times/week), KIDMED score and medicine were identified by review of the literature. The effect size was estimated by unstandardized β coefficient and 95% confidence interval. Statistical significance was set a priori at $p < 0.05$.

Results

At baseline, of the 72 children recruited, 54.2% (39) were male, 45.8% (33) were female, with a mean age of 7.97 ± 2.21 years, and 39.7% (27/68) were overweight/obese (BM1 $\geq$ 25 kg/m^2) with 48.6% (34) exercising at least three times per week and 83% (59) taking asthma medication daily. Girls were slightly more overweight/obese than boys [40.6% (13/32) vs. 38.9% (14/36) respectively; $p = 0.88$]. With respect to pulmonary function, in general, children had well-controlled asthma. Spirometry showed normal lung function (FVC, FEV_1, FEV_1/FVC, PEF $\geq$ 80% predicted, FEF 25–75% > 60–65%) and absence of bronchial inflammation (FeNO < 20 ppb). Baseline data is summarised according to BMI status (normal weight vs. overweight/obese) in Table 1.

There were weak positive correlations between BMI and FVC ($p = 0.013$, $\rho = 0.29$), FEV_1 ($p = 0.026$, $\rho = 0.26$) and $FEF_{25–75\%}$ ($p = 0.345$, $\rho = 0.11$). In contrast, a negative trend was observed between BMI and FEV_1/FVC, PEF and FeNO although non-significant. Stratification by sex showed a positive correlation between BMI and FVC ($p = 0.004$; $\rho = 0.49$) and FEV_1 ($p = 0.027$; $\rho = 0.38$) in girls; and a negative correlation between BMI and PEF in boys ($p = 0.049$, $\rho = -0.32$).

Univariate analysis showed no difference in spirometry parameters between normal weight and overweight/obese groups ($p > 0.05$). Contrastingly, there was a statistically significant difference in FeNO between the overweight/obese and the normal weight groups ($p = 0.027$). Median FeNO was slightly lower in the overweight/obese group as compared to the normal weight group (median 5 vs. 11 ppb respectively; $p = 0.027$) (Fig. 1).

No effect on BMI group was observed for FEV_1, FVC, FEV_1/FVC, PEF, FeNO in the unadjusted and adjusted models ($p > 0.05$). As for $FEF_{25–75\%}$, in the unadjusted model no difference was noted between BMI groups ($p = 0.40$, $\beta = 4.363$, 95% CI −6.00–14.73). However, after controlling for confounders namely age, height, sex, regular physical activity, medication and KIDMED score, a positive effect of overweight/obese on $FEF_{25–75\%}$ was observed (Table 2). $FEF_{25–75\%}$ increased by 11.65 units for children in

Table 1 Baseline subject characteristics and lung function for total sample and summarised by BMI group

Variable	Total	BMI Group				p value
		Normal		Overweight/obese[1]		
		Mean (n)	SD	Mean (n)	SD	
Male	54.2% (39)	53.7% (22)		50.00% (14)		0.88[c]
Age	7.97 ± 2.21	7.83	2.38	8.33	1.98	0.23[b]
BMI	18.34 ± 3.74	16.49	1.74	21.93	3.23	**0.00[b]**
FVC (L)*	95.11 ± 9.87	93.29	9.17	97.63	9.92	0.07[a]
FEV_1 (L)	97.67 ± 10.16	95.95	9.98	100.41	10.70	0.08[a]
FEV_1/FVC	102.01 ± 6.40	102.17	6.51	102.04	5.61	0.93[a]
PEF (L/s)	94.65 ± 19.11	93.95	19.09	93.59	14.58	0.93[a]
$FEF_{25–75\%}$	102.06 ± 20.88	100.41	21.49	104.78	20.08	0.40[a]
FeNO (ppb)	13.59 ± 13.36	15.35	12.33	11.44	15.33	**0.03[b]**
FeNO < 20 ppb	76.1% (54)	70.00% (28)		85.71% (23)		0.15[c]
Regular exercise ≥ 3 times/week	48.6% (34)	46.15% (18)		50.00% (14)		0.65[c]
Asthma medication over past month yes	83.1% (59)	82.93% (34)		81.48% (22)		0.86[c]

Bold character represents significant p-values. BMI group: normal weight (n = 41), overweight/obese (n = 27)

BMI body mass index, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *FEV_1/FVC* ratio of forced expiratory volume in 1 s and forced vital capacity, *PEF* peak expiratory flow, *$FEF_{25–75\%}$* mid expiratory flow 25–75% vital capacity, *FeNO* fractional exhaled nitric oxide

*% Predicted pre-bronchodilator; p-value significant at the 5% level

[1]Overweight/obese refers to combined data for overweight and obese subjects

[a]p value calculated using independent t test

[b]Mann–Whitney test

[c]Chi Square test

the overweight/obese group as compared to normal weight ($p = 0.043$; $\beta = 11.65$ units, 95% CI 0.36–22.94).

Discussion

In this report, we demonstrated a positive association of overweight/obesity on dynamic lung volume represented by $FEF_{25–75\%}$, an indicator of small airway calibre, which is consistent with the literature [10]. This is clinically significant because small airway function has been associated with asthma symptoms (dyspnoea), impaired control and health-related quality of life [11]. No significant association of weight status was detected for FeNO in the adjusted regression model controlling for age, height, sex, regular physical activity, medication and KIDMED score. Most studies have examined the effect of BMI on FEV_1, FVC and FEV_1/FVC [1]. Our finding is novel and adds to the limited evidence on the impact of body weight on lung function in small airways in asthmatic children. To our knowledge, this is the second study since that undertaken by Spathopoulos in 2009 to investigate the relationship between overweight, lung function and FeNO in Greek asthmatic school children [12]. The finding of a positive association of excess weight on lung volume and airway flow as reflected by increments in FEV_1, FVC and $FEF_{25–75\%}$ in overweight/obese children as compared to the normal weight has been documented in prior paediatric studies [10, 13–16]. The sex effect might be because of the earlier growth spurt and onset of puberty in girls as compared to boys [16]. As for biomarkers of airway limitation, FEV_1/FVC and PEF, a negative correlation was observed although it is non-significant, most likely due to small sample size. Further studies with larger samples are warranted to clarify this association.

Recently, Ekstrom et al. demonstrated that overweight/obesity was associated with increased lung volume (FVC, FEV_1) and airway obstruction (reduced FEV_1/FVC) in children up to 16 years [13]. Jones et al. found an increase in FVC and FEV_1 by 13.6% and 7.6% respectively as well as a 3.5% reduction in FEV_1/FVC in overweight asthmatic children [15]. Comparable results were described by Yao et al. in the PATCH study [10]. BMI disproportionately increased FVC, FEV_1, PEF and $FEF_{25–75\%}$ but decreased FEV_1/FVC and FeNO in Asian children. However, in contradiction to

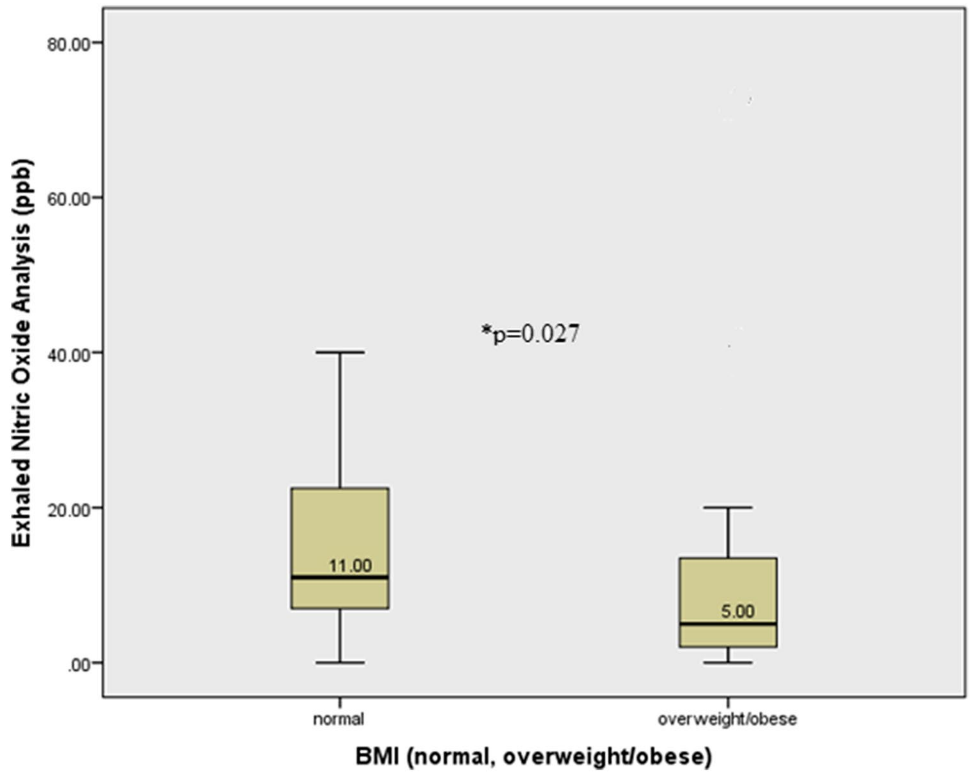

Fig. 1 Box-plot of FeNO versus BMI group. It is apparent that median FeNO was lower in the overweight/obese group than in the normal weight group (5 vs .11 ppb respectively, $p=0.027$). *Mann–Whitney test

Table 2 Adjusted multiple linear regression model

Spirometry parameter	Co-variate	β	95% CI	*p* value
FEF $_{25–75\%}$	BMI group	11.65	0.36, 22.94	**0.043**
	Age	3.59	−2.10, 9.27	0.21
	Height	−0.76	−1.76, 0.23	0.13
	Sex	−4.42	−14.65, 5.79	0.39
	Regular physical activity	−3.67	−14.21, 6.87	0.49
	Medication	3.74	−10.52, 18.00	0.60
	KIDMED score	−1.64	−4.19, 0.90	0.20

Bold character represents marginally significant *p*-values. *$FEF_{25–75\%}$* mid expiratory flow 25–75% vital capacity. Spirometry variables presented as percent predicted pre-bronchodilator administration

β Unstandardized coefficient, *95% CI* 95% confidence interval

*BMI as the dichotomous variable (overweight/obese vs. normal weight)

[a]*p* value evaluated applying multiple linear regression model controlling for confounders namely age, height, sex, regular physical activity, KIDMED score and medication

our findings, Spathopoulos et al. documented that high BMI reduced spirometry parameters, FVC, FEV_1, $FEF_{25–75\%}$ and FEV_1/FVC, in overweight/or obese Greek school children [12]. Discrepancies among studies could be due to variability in sample size, age, population diversity, ethnicity, asthma definition and tools used to assess adiposity in children (BMI, waist to hip ratio, % body fat).

With respect to the absence of airway limitation as reflected by FEV_1/FVC, a feasible explanation could be that abnormal lung growth caused by surplus weight could be a consequence of high BMI and not indicative of airway dysfunction. Then again, there were only seven obese children in our sample. Therefore, any expected decline in spirometric parameters due to large increases in fat mass would have been underpowered to detect any significant differences. Also, the apparent discrepancy between changes in forced volumes and their ratio in obese children could be attributed to the variable effect of weight according to the degree of overweight. It has been suggested that obesity may affect spirometry measurements when BMI ≥ 40 kg/m^2 [17]. The highest value for BMI in our children was 30.61 kg/m^2.

One potential mechanism by which overweight could impact lung function in asthmatic children is that excess bodyweight promotes disproportionate or abnormal lung growth represented by a mismatch between growth of airways and that of lung parenchyma that is manifested as high or supranormal FVC, FEV_1 and $FEF_{25-75\%}$ but decreased FEV_1/FVC (indicative of airway obstruction) [10]. Airway dysanaptic growth or large lung size is also seen in swimmers, which does not have any association with lung disease [18]. The above-mentioned findings have important implications in the interpretation of lung function tests because spirometry may have reduced specificity and sensitivity for asthma in overweight paediatric patients. In addition, most of the studies linking obesity and lung function in children are based on spirometry which mainly reflects large airway function [19]. Impulse oscillometry may be more appropriate to measure lung resistance and reactance ('true' obstruction) in peripheral and central airways as well as to confirm the presence of dysanapsis in patients with obese-asthma phenotype, as was done in the study by Ekstrom et al. (2018) [13, 19]. Application of impulse oscillometry to analyse the 'true obstructive disorder' as compared to spirometry deserves further investigation.

FeNO is established as a robust non-invasive biomarker of eosinophilic airway inflammation [9]. With respect to low FeNO measurements in overweight/obese asthmatic children as compared to normal weight or no associations, these results might primarily originate from differences in airway calibre or lung volumes between the two groups. Our findings might be related to anatomical and mechanical obstructive effect on airways that favour a ventilation perfusion imbalance rather than a result of inflammation [14]. This paradox/anomaly of low or no relationship between FeNO and BMI has been documented by prior cross-sectional studies in children [10, 13, 20, 21]. Collectively, these revelations suggest that increased adiposity might lead to neutrophilic rather than eosinophilic systemic inflammation [14]. Nevertheless, we did not measure blood neutrophil or eosinophil cell count in the present study. Additionally, reduced FeNO might be the result of limited production of NO in the airways as well as increased NO metabolism [22]. Excessive fat leads to an increase in arginase expression relative to L-arginine concentration and subsequently to lower FeNO levels [22].

A limitation of this study is small sample size. Our findings are based on cross-sectional data, and a causal relationship cannot be inferred. Although BMI is not the gold standard to assess body composition, most studies investigating the obesity-asthma link have used BMI as a proxy for total body fat and to monitor changes in body composition. Lung volume decline is related to 'fat distribution' which comprises of central and peripheral fat as well as tissue composition [17]. Most of the fat deposits in central obesity are in the abdominal area and excessive accumulation of fat mass can alter the pressure–volume characteristics of the thorax and restrict the descent of the diaphragm leading to limited lung expansion [17]. Abdominal adiposity as measured by waist circumference and waist/hip ratio might be better predictors of pulmonary function than weight or BMI [17]. Despite adjusting main confounders in the multivariate analyses, we cannot exclude that pulmonary test measurements could be affected by residual or unmeasured factors that have not been controlled (such as social economic status, maternal smoking or education level). In conclusion, the findings of this study suggest that excess bodyweight could impact pulmonary dynamics in childhood asthma. Future studies are recommended to establish the underlying mechanism behind the obesity and asthma link.

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Author Contributions MMP conceptualized, designed and drafted the manuscript, collected data and performed the statistical analyses. CI was in charge and co-ordinated the study. BE supervised the statistical analyses and interpretation of data. All co-authors critically revised, edited the manuscript and approved the final version as submitted. The authors confirm that the article is the authors' original work, has not received prior publication, and is not under consideration for publication elsewhere.

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Compliance with Ethical Standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institution (La Trobe University Human Ethics Committee, HEC 16-035) and with the 1964 Helsinki declaration and its later amendments.

Informed Consent Informed consent was obtained from all individual participants included in this study.

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