Original Article
EPIDEMIOLOGY/GENETICS

Obesity

Associations of Body Fat Percent and Body Mass Index with Childhood Asthma by Age and Gender

Panayiotis K. Yiallouros[1], Demetris Lamnisos[1,2], Ourania Kolokotroni[1], Maria Moustaki[3] and Nicos Middleton[2]

Objective: High body mass index (BMI) has been shown to be associated with asthma, but the pattern of this association is still unclear and may differ by gender or stage of puberty. BMI is only a proxy of adiposity, whereas estimation of body fat percent (BF%) by the bioimpedance technique is considered an accurate measure of adiposity. We investigated whether BMI and BF% behave differently in their association with asthma between genders, before and during adolescence.

Design and Methods: In this cross-sectional study of 10,981 schoolchildren, we used logistic regression models to examine the pattern of association of BMI and BF% with asthma.

Results: In the case of BF%, both the highest (odds ratio [OR]: 1.68, 95% confidence interval [95% CI]: 1.21-2.30) and lowest (OR: 1.59, 95% CI: 1.13-2.23) *z*-score categories conferred an increased adjusted risk for active asthma. The likelihood ratio test (LRT) of nonlinearity yielded significant results ($P < 0.01$) for BF%. In contrast, the LRT for BMI yielded a nonsignificant result ($P = 0.45$) indicating a linear association of asthma with BMI. A unit increase in BMI *z*-score conferred an increase in the adjusted odds of active asthma (OR: 1.14, 95% CI: 1.02-1.27). In the case of BF%, the adjusted ORs for active asthma at the highest and lowest *z*-score categories in both genders, before and during adolescence, were similarly elevated, exhibiting a U-shape pattern.

Conclusions: In contrast to the linear association observed with BMI, BF% displayed a U-shaped association with asthma and may be the preferred measure of adiposity in epidemiological studies of asthma in children.

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Introduction

In recent decades, the prevalence of asthma and obesity in the developed world has been increasing and, to date, several studies from North America, Western Europe, and Asia have shown associations between high body mass index (BMI) and asthma in both adults and children (1-8). Yet, the precise pattern of the relation of obesity with asthma is not clear (7). A review of the literature suggested that most studies (9) have focused on high BMI and shown associations with asthma, mainly in girls and women (10-12). Nevertheless, some studies have reported an increased risk of asthma amongst the underweight, whereas others have reported nonlinear, U-shape associations with BMI, at least in men and boys (4,13-18). Furthermore, some studies found no association between BMI and asthma in early childhood but only after the onset of puberty or during advanced adolescence (10,12). Castro-Rodriguez et al. found that girls who became overweight between ages 6 and 11 were more likely to have new asthma symptoms at age 11 or 13, whereas a similar association was not observed in boys (10). Gold et al. reported that a higher baseline BMI and a greater increase in BMI were associated with developing asthma in 6- to 14-year-old girls followed for 5 years. The association in boys was more complex, with both the smallest and greatest changes in BMI being associated with asthma (11).

The inconsistent findings regarding the pattern (i.e., linear vs. nonlinear) of the relation between BMI and asthma and the discrepancies in the behavior of the association between males vs. females and between preadolescent vs. adolescent children may be at least partly attributable to exposure misclassification bias. BMI is only a proxy indicator of adiposity and the degree of correlation with adipose tissue changes with age (19). It is also known that for a given BMI, women have a greater percentage of body fat than men. In addition, it has been proposed that females are more likely to develop asthma after puberty, because it is then they have a significant increase in body fat (12). A few studies have used direct measures of fat such as skin fold thickness or formulas using skin fold

[1] Cyprus International Institute for Environmental & Public Health in Association with Harvard School of Public Health, Cyprus University of Technology, Limassol, Cyprus. Correspondence: Panayiotis K. Yiallouros (p.yiallouros@cut.ac.cy) [2] Department of Nursing, School of Health Sciences, Cyprus University of Technology, Limassol, Cyprus [3] 3rd Department of Pediatrics, Attikon University Hospital, Athens, Greece

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measures to investigate the relation of body fat and asthma, but there were no agreed cutoff values for these measures and their findings have generally been inconsistent (20-22). Estimation of body fat percent (BF%) by the bioimpedance technique is a valid method of assessing body fat and has good correlation with measurements by the dual-energy X-ray absorptiometry (DEXA) method (23,24). Nevertheless, body composition methods rely on assumptions that may vary among different ethnic population groups. In relation to this, BF%, as estimated by bioimpedance analysis, differs between ethnic groups and this may lead to misclassification of obesity or underweight if not adequate cutoff points for body fat are not obtained from the different ethnic population groups (25,26). To date, BF% measured by bioelectrical impedance has been used in only two epidemiological studies, both reporting significant positive associations with asthma (27,28).

The primary aim in this study was to investigate the pattern of the association of asthma with two measures of adiposity (i.e., BMI and BF%) in school-age children. Furthermore, we aimed to examine the extent to which BMI and BF% exhibit a different pattern of association with asthma by gender as well as across different stages of adolescence.

Methods and Procedures

Study population

As part of a broader study of pediatric respiratory health in Cyprus during the academic year 2007-2008, we addressed a large number of schoolchildren belonging to four distinct age groups, from the preadolescent stage up to completion of adolescence. We assessed the prevalence of respiratory symptoms and asthma and measured both BMI and BF%. Study participants were recruited from the school setting and belonged to the following age groups: (a) second grade of primary school (7-8 years, Group A), (b) second grade of secondary school (13-14 years, Group B), (c) fourth grade of secondary school (15-16 years, Group C), and (d) fifth grade of secondary school (16-17 years, Group D). Approval for this study was obtained from the National Bioethics Committee of Cyprus.

Assessment of outcome variables

Prevalence of respiratory symptoms and asthma was assessed using the Greek version of the International Study of Asthma and Allergies (ISAAC) standardized questionnaire. The core questionnaire was enriched with questions on demographic and lifestyle covariates and was completed by the parents in the case of the younger children (Group A), whereas in all other cases (Groups B-D) it was self-completed by the children during school visits, after written informed consent was obtained from their parents. Using a combination of answers to two basic questions of the ISAAC questionnaire, we defined active asthma, the main outcome of the study, as report of ever having asthma and report of wheezing in the past 12 months.

Assessment of predictor variables

Trained research assistants performed the anthropometric measurements during visits at the children's schools after written informed consent was obtained from the parents. Height was measured twice with a portable Seca stadiometer 208 (Vogel & Halke GmbH & Co, Hamburg, Germany) to the nearest centimeter. Weight and body composition in water and fat % were measured twice with the help of Bio-Impedance Analysers (Tanita TBF-300). Measurements were taken after breakfast using a standard protocol, which required the subject to be barefoot and dressed in light clothing. For all the anthropometric parameters, the mean value of the two measurements was used in the analyses. We expressed both BMI (kg/m^2) and BF% as age- (Groups A-D) and gender-specific *z*-scores calculated using each of the eight subgroups' respective mean values and SDs.

Statistical analysis

Student's independent sample *t*-tests were used for binary comparisons of continuous variables (i.e., BMI and BM% measurements) and chi-square tests were used for binary comparisons of categorical variables (i.e., report of active asthma). Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence interval (95% CI) of active asthma across categorical and continuous levels of age- and gender-specific *z*-scores of BMI and BF%. Because of the high correlation between BF% and BMI in the dataset, we did not include both in the same logistic regression models. On the basis of the age- and gender-specific *z*-scores of BMI and BF%, five categories were defined in terms of SDs from a middle (reference) category, i.e., first ≤ -1 SD, second (-1 to -0.5 SD), third (-0.5 to 0.5 SD), fourth (0.5 to 1 SD), and fifth ≥ 1 SD. The extent of nonlinearity in the observed associations was assessed using likelihood ratio tests (LRTs) comparing models including the predictor variables as categorical terms (namely, five categories) vs. models including the categories as a linear term (i.e., estimating a summary linear effect per category increase). As such, a significant test result indicates evidence of deviation from a stepwise linear increase across categories of BMI or BF%. In the case of a nonsignificant result, we also performed logistic regression against the predictor as a continuous variable; otherwise, only ORs across categorical levels of the predictor were reported. In addition to gender and age group (Groups A-D), all models adjusted for active smoking (i.e., report of current smoking by the subject) and passive smoking (i.e., report of current smoking by father, mother, or any other person in the household) that are known strong predictors of respiratory outcomes. All models tested for interaction of the predictors under study by gender or across the different age groups. We have also tested for a three-way interaction between both gender and age and either of the two predictors. In all cases, evidence of effect modification was assessed in LRTs comparing models with and without the interaction terms. All analyses were performed using the R statistical software (29). Significance tests and confidence intervals were calculated at a significance level of 5%.

Results

Descriptive analyses

A total of 10,981 children took part in the respiratory health survey (out of 29,909 invited, 36.7% response rate). The number of participants from each of the four age groups was as follows: Group A (7-8 years): $n = 2{,}217$, Group B (13-14 years): $n = 2{,}452$, Group C (15-16 years): $n = 2{,}881$, and Group D (16-17 years): $n = 3{,}431$. Table 1 presents the characteristics of the participants along with unadjusted prevalence estimates of the study outcomes. Of note is the small overrepresentation of females in the secondary school groups (Groups B, C, and D) as opposed to the almost equal

TABLE 1 Summary statistics for study outcomes (means and 95% CI) and predictor variables (frequency and 95% CI) across the eight age- and gender-specific study groups

	Group A Aged 7-8 years		Group B Aged 13-14 years		Group C Aged 15-16 years		Group D Aged 16-17 years	
Variable	Female ($n = 1,094$)	Male ($n = 1,112$)	Female ($n = 1,269$)	Male ($n = 1,181$)	Female ($n = 1,591$)	Male ($n = 1,290$)	Female ($n = 1,897$)	Male ($n = 1,534$)
Current wheezing (%)	6.2 (4.9, 7.8)	11.2† (9.4, 13.2)	3.8 (2.9, 5.0)	4.4 (3.3, 5.7)	5.6 (4.5, 6.8)	5.3 (4.2, 6.7)	5.8 (4.8, 6.9)	6.9 (5.7, 8.3)
Diagnosis of asthma (%)	14.4 (12.5, 16.7)	20.8† (18.5, 23.3)	11.0 (9.4, 12.8)	11.6 (9.9, 13.6)	12.3 (10.8, 14.0)	11.7 (10.1, 13.6)	10.0 (8.8, 11.5)	12.0 (10.5, 13.8)
Active asthma (%)	4.0 (3.0, 5.4)	7.3† (5.9, 9.0)	2.0 (1.3, 2.9)	2.6 (1.8, 3.6)	1.9 (1.3, 2.7)	2.4 (1.7, 3.4)	2.1 (1.5, 2.8)	2.2 (1.5, 3.0)
Passive smoking (%)	39.1 (36.2, 42.1)	41.1 (38.3, 44.1)	52.6 (49.8, 55.4)	49.2 (46.3, 52.1)	53.6 (51.1, 56.1)	51.8 (49.0,54.6)	56.4 (54.1,58.7)	53.1 (50.5, 55.6)
Active smoking (%)	N/A	N/A	1.1 (0.7, 1.9)	2.2 (1.5, 3.2)	5.3 (4.3, 6.5)	13.1† (11.3, 15.1)	11.0 (9.6, 12.5)	23.5† (21.4, 25.7)
Family history of allergies (%)	36.7 (33.8, 29.6)	37.6 (34.8, 40.5)	18.5 (16.5, 20.8)	14.5† (12.5, 16.6)	24.5 (22.4, 26.7)	14.1† (12.3, 16.1)	22.9 (21.0, 24.8)	16.3† (14.5, 18.2)
BMI (mean)	17.2 (17.0, 17.3)	17.3 (17.1, 17.5)	21.0 (20.8, 21.2)	21.4* (21.2, 21.7)	21.8 (21.6, 21.9)	22.7* (22.5,23.0)	22.0 (21.8, 22.2)	23.4* (23.2, 23.7)
BF% (mean)	20.5 (20.0, 21.1)	19.9 (19.5, 20.3)	26.9 (26.5, 27.4)	17.5* (17.1, 18.0)	27.8 (27.5, 28.1)	16.8* (16.3,17.2)	26.6 (26.3,26.9)	16.5* (16.2,16.9)
Correlation coefficients between BMI and BF%**	0.87‡	0.92‡	0.84‡	0.86‡	0.84‡	0.88‡	0.79‡	0.85‡

N/A, not applicable.
†*P*-value < 0.05 for chi-squared test comparing the proportions between females and males within each age-group.
**P*-value < 0.05 for independent sample *t*-test comparing the means between females and males within each age group.
**Pearson's correlation coefficients.
‡*p*-value of Pearson's correlation < 0.05.

participation of both genders in the primary school group (Group A). The unadjusted prevalence rates for active asthma were 5.7, 2.3, 2.1, and 2.7% in Groups A, B, C, and D, respectively. Active asthma was more prevalent in boys (7.3 vs. 4.0%) in the 7-8 years age group but there was no difference in prevalence in the adolescent age groups. Statistically significant differences were also observed across the four age groups in terms of all the predictor and outcome variables (all *P*-values < 0.01). With the exception of active smoking and BMI, pair-wise comparisons suggest that this is generally driven by the larger difference seen between the younger age group with each of the older three age groups (Table 2). With respect to active smoking and BMI, a clearly increasing pattern was observed across the different age groups that resulted in all pair-wise differences being found statistically significant (Table 2). Furthermore, passive exposure to tobacco smoke was much lower in the primary school group as opposed to the respective frequencies in the secondary school groups. It is unclear whether this represents a true population shift in smoking practices among parents of the younger cohort or this is a result of the different reporting methodology, because in the case of the primary school children it was the parents who completed the questionnaires as opposed to self-completion in the case of the older children. Boys of the two older age groups have been by far more frequently actively smoking than girls, whereas family history of allergies was more frequently reported by girls than boys in all three of the adolescent age groups. It is unclear if this represents a gender-related reporting bias or reflects a true discrepancy.

No significant difference was observed between 7- and 8-year-old males and females (Group A) either with respect to their BMI or their BF% values (Table 1). However, in the secondary school age groups, there were significant differences between males and females in terms of their mean BMI and BF% values. Although because of the large sample size even small differences attained statistical significance, as-expected gender differences were recorded in the pattern of change in BMI and BF% from the primary to the secondary school age groups. More specifically, in the case of males, BMI followed an increasing pattern rising from an average of 17.3 among 7- to 8-year-old children to 21.4, 22.7, and 23.4 in contrast to the decreasing pattern observed with BF% mean values from

TABLE 2 Multiple age groups (A–D) comparisons of means and proportions for predictor and outcome variables[1]

Variable	Pairs of age groups with significant differences
Sex	(A,C), (A,D), (B,D)
Current wheezing	(A,B), (A,C), (A,D), (B,D)
Diagnosis of asthma	(A,B), (A,C), (A,D)
Active asthma	(A,B), (A,C), (A,D)
Passive smoking	(A,B), (A,C), (A,D), (B.D)
Active smoking	(B,C), (B,D), (C,D)
Family histories of allergies	(A,B), (A,C), (A,D), (B,C), (B,D)
BMI	(A,B), (A,C), (A,D), (B,C), (B,D), (C,D)
BF%	(A,B), (A,C), (A,D), (C,D)

[1]The pairs of age groups having significant ($P < 0.01$) differences are shown inside the brackets.

19.9% to 17.5, 16.8, and 16.5% across the age span covered by the study population. In females, there was a concurrent increase of both BMI and BF% across age groups, even though the increase appeared relatively steeper in the case of BF%. Despite the gender-related differences in the pattern of changes of BMI and BF% from childhood to adolescence, the Pearson's correlation coefficients between BMI and BF% remained strong across all age groups. In both males and females, correlations were only slightly stronger in the younger age group (Group A) than in the older age group (Group D), i.e., 0.92 vs. 0.85 in males and 0.87 vs. 0.79 in females (see Table 1). In Table 3, we present the cutoff values corresponding to each BMI and BF% *z*-score categorical group (and the relative frequency of participants in each group) stratified by gender and age group to indicate where our population's distributions of BMI and BF% stand with regards to reference or other international populations.

The scatter plot of the two adiposity measures reflected the strong correlation of BMI and BF% although at the lower tail we observed a markedly higher scatter of the BF%-BMI values indicating a poorer correlation between them in this range of values (Figure 1).

Associations of active asthma with BMI and BF%

Table 4 presents raw prevalence estimates (and 95% CI) along with unadjusted and adjusted ORs (and 95% CI) of active asthma across categorical levels of BMI and BF% as estimated in logistic regression models. In all models, the central category (i.e., *z*-score values between −0.5 and 0.5) was used as the reference group. With respect to BMI, the highest ORs of active asthma were observed among participants with the highest *z*-scores before adjusting for covariates. Specifically, among those with BMI *z*-score $\geq$ 1, the unadjusted OR for active asthma was 1.49 (95% CI: 1.07-2.05) and attenuated slightly to 1.36 (95% CI: 0.97-1.88) after adjusting for gender, age group, and active and passive smoking in multivariable models. Consistent with this finding, a statistically significant and even stronger association with active asthma was observed amongst the category with the highest BF% *z*-scores. The unadjusted OR of 1.79 (95% CI: 1.30-2.44) attenuates only slightly in the adjusted models to 1.68 (95% CI: 1.21-2.30) and remained statistically significant. However, in the case of BF%, we also observed a statistically significant association with active asthma among participants with the lowest BF% *z*-scores even after adjusting for age group, gender, and covariates (OR: 1.59, 95% CI: 1.13-2.23). This was not the case with BMI where there was no evidence of increased risk of active asthma among participants with the lowest *z*-scores (i.e., first category). As shown more clearly in Figure 2, the association of BF% with active asthma exhibits a clear U-shape pattern unlike the monotonic increase observed in the case of BMI. In fact, in the case of BF%, there was strong evidence for nonlinearity in LRTs (*P*-value < 0.01) as a result of the steep increase in the ORs of active asthma observed both in the lowest and highest BF% *z*-score groups. In sharp contrast, LRTs provided no evidence of nonlinearity in the association of active asthma with BMI (LRT $P = 0.45$). Expressed in linear terms, the adjusted OR of active asthma per unit increase of BMI *z*-score was 1.14 (95% CI: 1.02-1.27; see Table 4).

Associations of active asthma with BMI and BF% stratified by gender and age group

To explore the nature of the association of the two measures of adiposity with asthma before and during adolescence, we merged the

TABLE 3 Cutoff values of each BMI and BF% *z*-score category (and relative frequency of participants in each group) by gender/age group

	Males								Females							
	Group A Aged 7–8		Group B Aged 13–14		Group C Aged 15–16		Group D Aged 16–17		Group A Aged 7–8		Group B Aged 13–14		Group C Aged 15–16		Group D Aged 16–17	
z-Score groups	Values	%	Values	%	Values	%	Values	%	Values	%	Values	%	Values	%	Values	%
BMI																
<-1	<14.6	10	<17.7	15	<19.1	14	<19.7	13	<14.5	14	<17.3	14	<18.5	15	<18.7	12
$-1, -0.5$	14.6, 15.8	26	17.7, 19.3	19	19.1, 20.7	20	19.7, 21.4	19	14.5, 15.6	21	17.3, 18.9	19	18.5, 19.9	18	18.7, 20.1	20
$-0.5, 0.5$	15.8, 18.5	36	19.3, 23.0	38	20.7, 24.3	36	21.4, 25.1	40	15.6, 18.3	35	18.9, 22.5	40	19.9, 23.2	40	20.1, 23.4	43
0.5,1	18.5, 20.0	9	23.0, 25.1	10	24.3, 26.4	12	25.1, 27.1	11	18.3, 19.8	11	22.5, 24.6	11	23.2, 25.0	12	23.4, 25.3	11
>1	>20.0	16	>25.1	17	>26.4	16	>27.1	15	>19.8	15	>24.6	15	>25.0	14	>25.3	14
BF%																
<-1	<13.8	12	<10.0	15	<9.9	15	<9.6	13	<12.0	15	<18.8	15	<21.1	15	<19.9	14
$-1, -0.5$	13.8, 16.2	22	10.0, 12.6	18	9.9, 12.3	15	9.6, 12.0	14	12.0, 16.3	17	18.8, 22.9	18	21.1, 24.5	15	19.9, 23.2	17
$-0.5, 0.5$	16.2, 22.1	36	12.6, 19.8	35	12.3, 19.0	38	12.0, 18.8	41	16.3, 24.8	34	22.9, 31.0	36	24.5, 31.1	39	23.2, 30.0	40
0.5, 1	22.1, 25.8	10	19.8, 24.9	13	19.0, 23.4	13	18.8, 23.4	15	24.8, 29.1	11	31.0, 35.0	14	31.1, 34.5	13	30.0, 33.3	13
>1	>25.8	17	>24.9	18	>23.4	17	>23.4	15	>29.1	16	>35.0	17	>34.5	15	>33.3	15

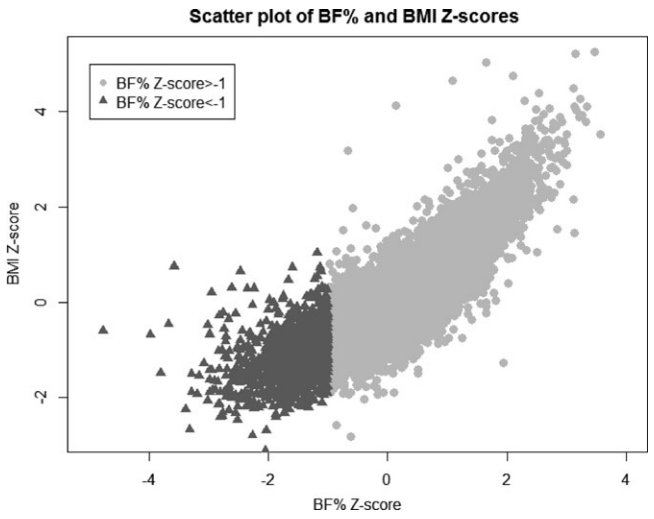

FIGURE 1 Scatter plot of BF% and BMI *z*-scores.

three secondary school groups and contrasted them with Group A (i.e., children 7-8 years of age). Figure 3 presents gender- and age-group-specific prevalence rates for active asthma across the *z*-score categories of BMI and BF%. Although there was a suggestion that the U-shape pattern of association between BF% and active asthma was stronger in preadolescence, and particularly amongst boys (the only group where a suggestion of U-shape pattern of association with BMI was also observed), the pattern appeared otherwise consistent across all study groups.

Evidence of effect modification by gender and age was assessed in LRTs comparing models with and without the interaction terms. There was no statistical evidence for a three-way interaction (*P*-value of LRT for three-way interaction = 0.45 and 0.78 for BMI and BF%, respectively); thus, Table 5 presents unadjusted and adjusted ORs of active asthma stratified by gender (and adjusted for age group) or stratified by age group (and adjusted for gender) along with the corresponding *P*-values for effect modification. In the case of BF%, the adjusted ORs for active asthma were similarly elevated in the highest and lowest *z*-score categories exhibiting a U-shape association in both genders. Although the pattern appeared rather stronger in males, the LRT for interaction by gender provided no evidence for effect modification ($P = 0.84$), suggesting that the observed pattern of association was consistent in both males and females. In the case of BMI, OR estimates greater than one were observed in the highest *z*-score category in both genders, but in the lowest *z*-score category the OR estimates were in opposite directions, with an OR for active asthma greater than one in males and an OR less than one in females; nevertheless, there was no evidence of effect modification by gender (*P*-value of LRT = 0.63).

In exploration of the effect of adolescence, elevated ORs of active asthma were observed in the highest and lowest BF% *z*-score categories in both the preadolescent and adolescent children. Although the estimated OR appeared rather higher in the lowest BF% *z*-score category in the preadolescent children, the LRT of interaction provided no evidence that the observed pattern was statistically different between preadolescent and adolescent children (*P*-value = 0.64), suggesting that a U-shape pattern of association of active asthma with BF% characterizes both stages, before and during adolescence. In contrast, no such U-shape pattern of association was observed in the case of BMI. Even though a stepwise elevation in the association of active asthma with BMI was clearly more evident in the case of

TABLE 4 Active asthma across (a) *z*-score categories of BMI and BF% and (b) per unit increase in *z*-score

	z-Score categories (range of values)					*P*-value for LRT[1]	Per unit increase in *z*-score[2]
	First (≤ -1)	Second (-1, -0.5)	Third (-0.5, 0.5)	Fourth (0.5, 1.0)	Fifth (≥ 1.0)		
BMI	n = 1,473 (13.4%)	n = 2,176 (19.8%)	n = 4,264 (38.9%)	n = 1,260 (10.9%)	n = 1,656 (15.1%)		
			Prevalence (%)				
	2.3 (1.6, 3.2)	3.0 (2.4, 3.8)	2.5 (2.1, 3.0)	3.5 (2.6, 4.7)	3.6 (2.8, 4.7)	–	–
			Unadjusted odds ratios				
	0.90 (0.60, 1.33)	1.21 (0.88, 1.66)	1.00	1.44 (0.99, 2.05)	**1.49 (1.07, 2.05)[3]**	0.23	**1.16 (1.04, 1.29)[4]**
			Adjusted odds ratios[5]				
	0.92 (0.61, 1.36)	1.10 (0.80, 1.51)	1.00	1.45 (1.00, 2.07)	1.36 (0.97, 1.88)	0.45	**1.14 (1.02, 1.27)[3]**
BF%	n = 1,574 (14.3%)	n = 1,839 (16.7%)	n = 4,155 (37.9%)	n = 1,418 (12.9%)	n = 1,764 (16.1%)	–	–
			Prevalence (%)				
	3.6 (2.8, 4.7)	2.4 (1.8, 3.2)	2.3 (1.9, 2.8)	2.8 (2.0, 3.8)	4.0 (3.2, 5.0)	–	–
			Unadjusted odds ratios				
	1.62 (1.16, 2.26)[4]	1.06 (0.73, 1.51)	1.00	1.23 (0.83, 1.78)	**1.79 (1.30, 2.44)[4]**	<0.01	–
			Adjusted odds ratios[3]				
	1.59 (1.13, 2.23)[4]	0.98 (0.68, 1.41)	1.00	1.28 (0.86, 1.86)	**1.68 (1.21, 2.30)[4]**	<0.01	–

[1]Likelihood ratio test for nonlinearity, comparing models with *z*-score categories as categorical vs. linear term.
[2]Association of active asthma expressed in terms of a unit increase in *z*-score. No estimate is presented in the case of BF% as there was evidence of nonlinearity.
[3]$P < 0.05$.
[4]$P < 0.01$.
[5]Adjusted for age group, sex, and active and passive smoking.

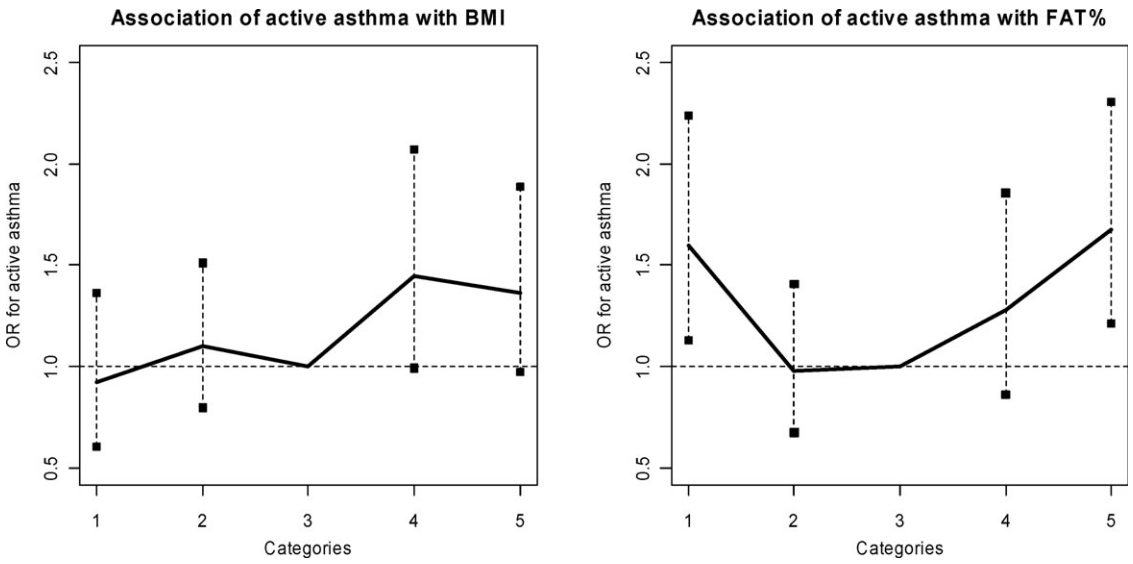

FIGURE 2 Adjusted odds ratios (and 95% CI) of active asthma across categorical levels of BMI and BF% *z*-scores.

adolescent children, there was no statistical evidence of interaction with age suggesting that the pattern of association does not differ in the case of the younger children (P-value = 0.51). This was further supported when BMI was modeled as a continuous variable along with possible interaction effects by gender and age, which also yielded no evidence that the overall linear association of active asthma with BMI differed by either gender (P-value for interaction = 0.81) or age group (P-value for interaction = 0.48).

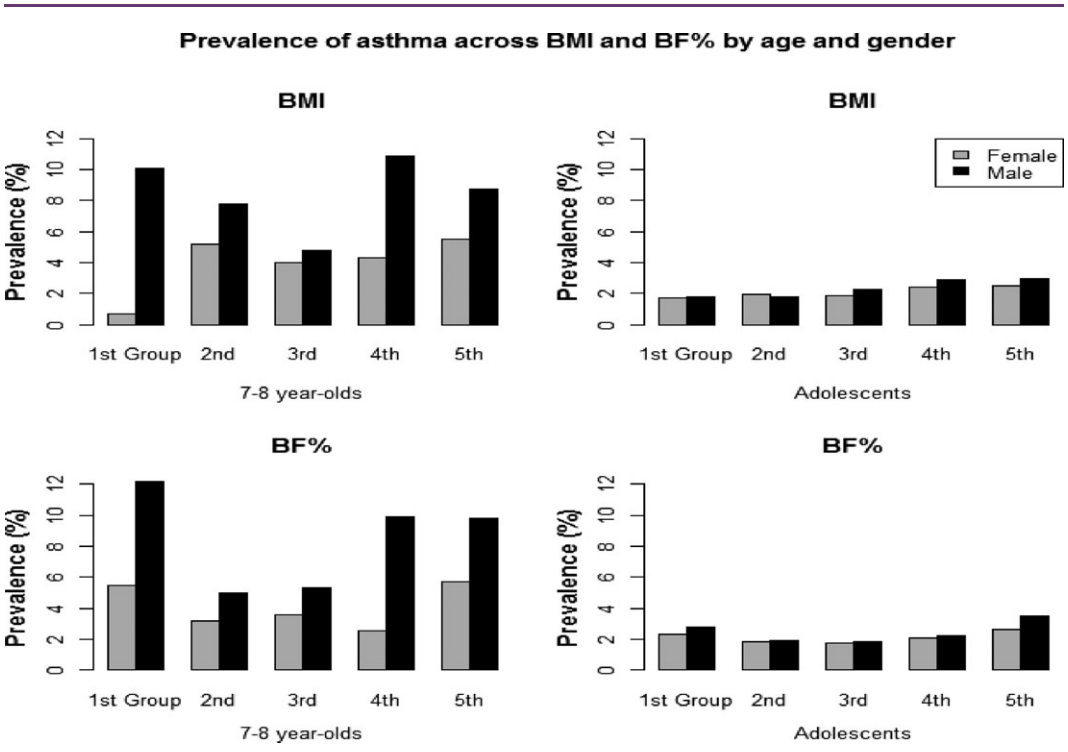

FIGURE 3 Prevalence of active asthma across *z*-score categories of BMI (top row) and BF% (bottom row), stratified by gender and age group (7- to 8-year olds vs. the rest).

TABLE 5 Active asthma[1] across BMI and BF% *z*-score categories by gender and age groups (7- to 8-year olds vs. all adolescents)

		z-Score categories (range of values)					
		First (≤ -1)	Second (-1, -0.5)	Third (-0.5, 0.5)	Fourth (0.5, 1.0)	Fifth (≥ 1.0)	*P*-value for LRT[2]
Stratification by gender							
BMI	Female	0.67 (0.34, 1.23)	1.12 (0.69, 1.76)	1.0	1.21 (0.69, 2.06)	1.26 (0.76, 2.03)	0.63
	Male	1.19 (0.70, 2.00)	1.10 (0.71, 1.70)	1.0	1.69 (1.03, 2.77)	1.46 (0.94, 2.29)	
BF%	Female	1.40 (0.84, 2.28)	0.99 (0.57, 1.67)	1.0	1.06 (0.58, 1.86)	1.45 (0.89, 2.33)	0.84
	Male	1.79 (1.12, 2.87)	0.98 (0.59, 1.62)	1.0	1.49 (0.89, 2.48)	1.89 (1.23, 2.91)	
Stratification by age groups							
BMI	Aged 7-8	1.19 (0.60, 2.35)	1.45 (0.68, 3.09)	1.0	1.16 (0.49, 2.73)	1.06 (0.48, 2.31)	0.51
	All adolescents	0.81 (0.48, 1.31)	0.87 (0.55, 1.32)	1.0	1.28 (0.80, 1.99)	1.25 (0.82, 1.87)	
BF%	Aged 7-8	2.14 (1.25, 3.68)	1.17 (0.53, 2.59)	1.0	1.62 (0.70, 3.75)	1.45 (0.71, 2.96)	0.64
	All adolescents	1.34 (0.85, 2.07)	1.05 (0.65, 1.66)	1.0	1.20 (0.73, 1.90)	1.64 (1.09, 2.45)	

[1]Results are adjusted odd ratios for age group or gender as appropriate as well as active and passive smoking in multivariable logistic models.
[2]Likelihood ratio test comparing models with and without interaction terms.

Discussion

In this large community study of preadolescent and adolescent schoolchildren, we have shown that BF% displays a U-shape association with active asthma as opposed to the linear association observed with BMI. The great majority of previous studies on the association of adiposity with asthma in children used BMI as the measure of exposure and focused specifically on the highest range of BMI values (9,30,31). Only a few studies have examined associations across the whole range of BMI values with some of them reporting a linear association of BMI with asthma (1,2,7) while others reporting a U-shape association with an increased risk of asthma in both the underweight and obese groups (15-18). In our study, the upper range of both measures of adiposity exhibited a positive association with asthma, which in fact appeared stronger in the case of BF% than in the respective BMI *z*-score category. Although the association of BMI with asthma appeared linear, suggesting that decreased BMI values are associated with decreased risk for asthma, in contrast we found evidence that low BF% *z*-score was also significantly associated with increased risk for active asthma. The scatter plot of BMI-BF% *z*-scores showed poorer correlation of the two measures of adiposity at the lower tail of the distribution. A number of previous studies have shown that BMI is not a good predictor of low body fat in adults and children (32,33) and this may also be the reason for the observed discrepancy in the pattern of association between asthma and these two measures of adiposity (BMI and BF%) at the low range of *z*-score values. In an effort to overcome these limitations of BMI, an alternative index of adiposity has been recently proposed based on hip circumference and height, which reflects more accurate BF% of males and females from different ethnicities without numerical correction (34). The usefulness of this new index remains to be assessed in future studies.

On the other hand, the estimates of BF% with bioimpedance analyzers, despite the good correlation with DEXA measurements, have been reported to have both systematic and magnitude biases (24) especially in subjects with extremely low or high adiposity, altered fat/lean mass ratios, and extreme heights and body shape abnormalities (35). This limitation clearly indicates the need for future studies with the inclusion of a gold standard measure of adiposity such as DEXA in order to define which of the two measures of adiposity (BF% or BMI) better reflects the association of asthma with adiposity.

When we examined the pattern of the association by gender, we found that BF% exhibited consistent positive association with asthma in the highest and lowest *z*-score categories in both genders. In contrast, in the case of the lowest BMI *z*-score category, the ORs, although not statistically different in this study, appeared elevated in males and reduced in females, which is consistent with the findings of several previous studies that reported low BMI to be associated with asthma particularly in males (4,11,16,17). Furthermore, BF% also demonstrated a consistent U-shape pattern of association with asthma in both preadolescent and adolescent children. Even though this pattern appeared more striking in the case of preadolescent children, there was no evidence that this was restricted to the younger children.

Four previous studies in children have looked into the association of body fat measures other than BMI with asthma (20-22,27). Garcia-Marcos et al. found high-range values of three measures of adiposity (namely, skin fold thickness, BF% estimates based on skin fold measurements, and BMI) to have a comparable increase on the odds for asthma (20). Figueroa et al. compared the highest with the lowest range of the sum of skin folds in a large number of children and reported an association with asthma only in girls and no evidence of nonlinearity in the observed association between asthma and BMI or across quintiles of the sum of skin folds (21). In contrast, though, in the study of Berntsen et al. in Tanzania, low sum of skin folds was found to be associated with increased asthma symptoms (22). The only pediatric study so far that used BF% estimation by the bioelectrical impedance method showed in 505 children aged 6-8 years that the highest quintile of BF% and BMI had a similarly positive association with asthma diagnosis when compared with the combined lowest two quintiles (27). The only other report to date that used BF% estimates with the bioelectrical impedance method was

performed in 1,000 young adults and found a positive association of BF% when expressed in linear terms with asthma but only in women. Although authors did not provide any statistical testing for nonlinearity of the asthma-BF% association, raw prevalence rates of asthma, as presented across quartiles of BF% in that study, suggest a U-shape pattern, particularly in men (28).

The main strength of our study is that it examines for the first time the association of BF% with asthma in a very large number of children throughout school age and provides adequate statistical testing indicating a nonlinear, U-shape pattern of association between active asthma and BF%, which appeared consistent in both genders as well as in the preadolescent and adolescent age groups. Although more studies are needed to replicate these findings, BF% estimation with the bioelectrical impedance method seems to have advantages as it is also easy to obtain, avoids the misclassification caused to BMI by varying amounts of muscle and bone mass in the two genders at the different age groups in childhood, and, based on the findings of this study, is yielding a more consistent pattern in the association of adiposity with asthma outcomes. Validity of bioelectrical impedance estimates has limitations in subjects at extremes of BMI ranges or with abnormal hydration and results in these cases should be interpreted with caution (35). However, in our study, the lowest (<-1) and highest (>1) z-score groups did not include only the very extremes of the BMI range and any random error in the estimates of BF%, resulting in exposure misclassification, would have pulled the associations toward unity. In contrast, strong associations have been observed here between BF% and asthma in both the highest and lowest BF% groups. The most widely accepted method of reference for the assessment of BF% is DEXA method that provides accurate estimates of bone mineral, lean soft tissue, and body fat. Nevertheless, this technique has the disadvantage of being cumbersome and requiring use of ionizing radiation (24).

Hormonal and proinflammatory (TNF-a and IL-6) mediators relating to adipose tissue have been proposed to explain the observed link between obesity and asthma (36). However, to date, there is still scant direct evidence in humans on the mechanisms through which systemic inflammation modulates the behavior of the asthmatic airway (6,8,37). Obesity also results in important changes to the mechanical properties of the respiratory system, which exert an additive effect to the asthma-related changes seen in the airways (6,8,37).

The reasons for the positive association of low BF% with asthma are not clear. Further research is warranted in this specific group of children to better elicit the physiological mechanisms involved. A previous study that used BMI as the measure of adiposity showed that underweight male students have a significantly lower peak and mid-expiratory flows in comparison with normal weight counterparts (27). Similarly, Schachter et al. (14) have reported that spirometric indices are significantly reduced in a low BMI (<18.5) group compared with a normal BMI group (18.5-24.9). In the study of McLachlan et al. (28), low BF% was associated with airflow obstruction in young men. It is possible that the impairment of lung function in subjects with poor nutrition, as reflected by low BMI and possibly by low BF%, may contribute to the appearance of asthmatic symptoms.

Another possible explanation is that both high and low adiposity make general health status worse, which as a result makes asthma more severe, or at least perceived as more severe, and thus lead patients to overreporting their asthmatic manifestations (30,31,38).

Our study has some limitations. First, the relatively low participation rate in the health survey amongst the targeted population precludes this article to serve as a report on the prevalence rates of both the adiposity measures and the asthmatic outcomes in the general population of schoolchildren. Nevertheless, there is no reason to believe that the participation of subjects in the survey was differentially affected by any of the predictor (BF% and BMI) and the outcome (asthma) variables (i.e., higher participation among asthmatics from the highest and lowest BF% as opposed to those in the middle range). In fact, the U-shape association of BF% with asthma was consistent across all age groups. Likewise, the pattern of association of BMI with asthma was consistent, albeit linear, in all age groups. This result cannot be simply attributed to selection bias, because there is no reason to believe that more asthmatics with lower BF% participated in the study rather than asthmatics with lower BMI. The definition of asthmatic status was based on responses to the ISAAC questionnaire and not on clinical parameters that would evidently be more reliable measures of asthma. However, in the context of this large community-based study, clinical data for such a large number of participants were not available and we essentially used epidemiological definitions for asthma as defined by the ISAAC protocol. Another potential limitation is the difference in reporting methods between the younger and the older age groups for asthma. Although, as per the ISAAC protocol, parental report was used in the case of young children and self-report for the older children to define asthma status, it has to be noted that the agreement between parental and self-report of asthmatic symptoms in children has been questioned in the past (39,40). Nevertheless, the consistent patterns of the observed associations of BF% and BMI with asthma in both the younger and older age group, irrespective of mode of reporting, are if anything reassuring and indicate that methods of reporting asthma did not affect the results in this study. Finally, any causal inferences between BF% and asthma are limited by the cross-sectional design of the study. The findings of this study suggest that, unlike BMI, BF% displays a clear U-shaped association with active asthma that is consistent in both males and females in preadolescent and adolescent schoolchildren.

In conclusion, BF% in addition to, if not as opposed to, BMI may be the preferred measure of exposure to be used in epidemiological studies exploring the association of adiposity with asthma in children. O

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