

The obesity–asthma link in different ages and the role of Body Mass Index in its investigation: findings from the *Genesis* and *Healthy Growth* Studies

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To cite this article: Guibas GV, Manios Y, Xepapadaki P, Moschonis G, Douladiris N, Mavrogianni C, Papadopoulos NG. The obesity–asthma link in different ages and the role of Body Mass Index in its investigation: findings from the *Genesis* and *Healthy Growth* Studies. *Allergy* 2013; **68**: 1298–1305.

Keywords

adiposity; association; asthma; Body Mass Index; children.

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Accepted for publication 25 July 2013

DOI:10.1111/all.12245

Edited by: Michael Wechsler

Abstract

Background: To date, an obesity/asthma link is well defined in adults; however, the nature of such a link is obscure in children, partly due to Body Mass Index (BMI) limitations as a surrogate fat mass marker in childhood. We thus opted to investigate the association of adiposity with asthma in children of different ages, using several indices to assess fat mass.

Methods: Wheeze ever/in the last 12 months (current) and physician-diagnosed asthma were retrospectively reported via questionnaire by the parents of 3641 children, participating in two cross-sectional studies: 1626 children aged 2–5 (the *Genesis* Study) and 2015 children aged 9–13 (the *Healthy Growth* Study). Perinatal data were recorded from the children's medical records or reported by parents. Anthropometric measurements (i.e., BMI, waist/hip circumference, biceps/triceps/subscapular/suprailiac skinfold thickness) were conducted in both cohorts; bioelectric impedance analysis (BIA) was conducted only in preadolescent children.

Results: In children aged 2–5, asthma was positively correlated with conicity index, waist/hip circumference, waist-to-height ratio, skinfold thickness, and skinfold-derived percentage fat mass ($P < 0.05$) but not BMI or BMI-defined overweight/obesity, after adjusting for several confounders. In children aged 9–13, asthma was positively associated with conicity index, waist circumference, waist-to-height ratio, skinfold thickness, skinfold-derived percentage fat mass, BIA-derived percentage fat mass, BMI, and BMI-defined overweight/obesity, following adjustment ($P < 0.05$). Current/ever wheeze was not consistently associated with fat mass in either population.

Conclusions: Fat mass is positively linked to asthma in both 2–5 and 9–13 age spans. However, the failure of BMI to correlate with preschool asthma suggests its potential inefficiency in asthma studies at this age range.

Asthma and obesity are important public health concerns and they both show a considerable rise in prevalence in the last 20 years, a trend implying a potential interrelation of their developmental mechanics (1–3). Prevalence of overweight and obesity in childhood is reaching epidemic proportions, as worldwide there are more than 40 million overweight or obese children below the age of 5 (4). Accordingly, pediatric asthma prevalence has been on the rise; currently, asthma is the most common chronic childhood disease in many industrialized countries (5). These trends emphasize the need to clarify the

relation of obesity with asthma. Nevertheless, although such a link has been well documented in adults, it has been less consistent in children, hampered in part by age-dependent definitions of overweight and obesity (2).

Proposed theories addressing the link between obesity and asthma involve obesity-related inflammatory mediators and comorbidities, oxidant stress, and mechanical chest restriction (4). However, disentangling this link in childhood is onerous, as obesity and overweight are challenging to define in pediatric patients. Although Body Mass Index (BMI) is recommended

by the World Health Organization as a classification tool (6), it fails to effectively distinguish lean from fat mass (7). This is an important consideration, as lean mass could have beneficial effects on lung function (as opposed to fat mass) (7). This distinction is rendered more important in childhood, due to complex BMI-independent growth-related shifts in fat distribution (8). This presumed BMI caveat could interfere with investigations on the asthma/obesity relation in children, whereas other potentially more accurate markers could be more suitable (8).

Currently, the nature of the relationship between obesity and pediatric asthma is obscure. Furthermore, it has been recently shown that indicators of central obesity – as opposed to BMI percentiles – are better associated with childhood asthma; however, data are scarce (8). We therefore hypothesized that adiposity is associated with asthma throughout childhood and that the capacity of BMI to uncover this link may be impoverished by age-dependent differences in fat mass deposition. Thus, we sought to investigate the pediatric asthma/adiposity relation and its potential dependence on age in two cohorts of children of different ages, using a plethora of alternative markers to assess regional and total body fat mass. Thereby, we concurrently appraised the relevance of BMI to these markers and its efficiency as a tool in pediatric asthma studies.

Methods

Study design

Participants

The *Genesis* Study is a cross-sectional analytical study carried out between 2003 and 2004; it involved children aged 2–5 attending nurseries within the counties of Attica, Aetoloakarnania, Thessaloniki Halkidiki, and Helia in Greece (9). The *Healthy Growth* Study is a cross-sectional analytical study, carried out between 2007 and 2008; its population comprises schoolchildren aged 9–13, attending primary schools within the Greek counties of Attica, Aetoloakarnania, Thessaloniki, and Iraklio (10). In both studies, sampling of nurseries/schools was random, multistage, and stratified by parents' educational level and the municipality's total student population, as previously described (9, 10). These regions represent north (i.e., Thessaloniki, Halkidiki), central (i.e., Attica), western (i.e., Aetoloakarnania), and southern (i.e., Iraklio, Helia) Greece; over 70% of the total Greek population resides there (Census 1999). Each study's population was therefore representative of the children of the respective age span. A number of nurseries and primary schools, selected randomly, were invited. A detailed letter describing the aims of each study and a consent form were provided to all parents or guardians of children. The study was approved by the Greek Ministry of National Education and the Ethics Committee of the Harokopio University of Athens.

Sociodemographic, maternal, and perinatal information

Sociodemographic and perinatal data were either reported by parents or extracted from birth certificates examined during school interviews. A standardized questionnaire was used to assess demographic characteristics and collect information on

factors that have been reported in the literature to possibly interfere in evaluation of asthma/wheeze-related outcomes. These include the following: (i) maternal smoking during pregnancy; (ii) parity; (iii) children's feeding practices from birth to 6 months of age (i.e., breastfeeding, mixed or exclusive *vs* no breastfeeding); (iv) maternal and paternal years of education stratified into: <9 years; 9–12 years; and more than 12 years; and (v) child's nationality (both parents Greek *vs* either parent non-Greek). Moreover, birthweight and gestational age were recorded from birth certificates and were used for classification into small for gestational age (SGA, < 10th percentile), appropriate for gestational age (AGA, 10–89th percentile), and large for gestational age (LGA, ≥ 90th percentile).

Asthma-related questions were derived from the ISAAC core questionnaire. We studied the following parent-reported outcomes: (i) current wheeze (Has your child had wheezing or whistling in the chest in the past 12 months?); (ii) ever wheeze (Has your child ever had wheezing or whistling in the chest at any point in time?); (iii) asthma ever (Has your child ever had asthma diagnosed by a doctor?).

Anthropometric indices and physical examination

Standardized equipment and protocols were used for all measurements. Physical examination entailed somatometric measurements (weight, height, and waist/hip circumferences) and skinfold thickness-mediated body fat assessment at four sites (biceps, triceps, subscapular, and suprailiac skinfolds). Weight was recorded to the nearest 10 g with a Seca digital scale (Seca Alpha, Model 770, Hamburg, Germany). Height was measured to the nearest 0.1 cm by a commercial stadiometer (Leicester Height Measure, Invicta Plastics Ltd., Oadby, Leicestershire, UK). BMI was assessed via Quetelet's equation ($\text{weight [kg]} / \text{height}^2 [\text{m}^2]$) and converted into age- and gender-specific standard (*z*) scores (11). The International Obesity Task Force (IOTF) cutoff points were used to categorize participants as 'normal weight', 'overweight', and 'obese' (12). Percent fat mass was calculated in both studies from skinfold thickness via the use of published equations (13); bioelectric impedance analysis (BIA) was undertaken only in the *Healthy Growth* Study to further confirm the skinfold-derived percent fat mass findings in this cohort. BIA was carried out with an Akkern BIA 101, Akkern Srl., Florence (Italy), via the application of electrodes to the right hand, wrist, foot, and ankle with the subject supine and arms and legs at a 45° angle. Waist and hip circumferences were measured to the nearest 0.1 cm with a nonelastic tape (Hoechstmass, Germany), as previously described (9). Biceps, triceps, subscapular, and suprailiac skinfold thickness were measured on the right side of the body to the nearest 0.1 mm using a Lange skinfold caliper (Cambridge Scientific Industries Inc., Cambridge, MA, USA). Conicity index was calculated as $[\text{waist circumference} / 0.109 \times \text{square root (weight/height)}]$ (14).

Statistical analysis

All continuous anthropometric variables were transformed into standardized variables (*z*-scores) to facilitate interpretation

of the odd ratios. Spearman correlation coefficients (ρ) for nonparametric continuous variables were used to examine associations between BMI z -scores and the alternative adiposity indices. To test the relation of body fat mass indices with the outcome variables, multivariate logistic regression models were built for a wide array of confounding factors.

Each logistic regression model included one dependent variable (i.e., current/ever wheeze or asthma ever), one independent anthropometric variable, and the confounding covariates, that is, prenatal smoking, gestational age, birthweight, gender, parity, breastfeeding, passive smoking at home, nationality, and parental educational level. The confounders incorporated

Table 1 Descriptive data for both *Genesis* and *Healthy Growth* Study children, in conjunction to their responses to the main asthma/wheeze outcomes

	Total cohort population	'Yes' for current wheeze <i>n</i> (%)	'Yes' for ever wheeze <i>n</i> (%)	'Yes' for asthma ever <i>n</i> (%)
<i>Genesis</i> Study (2–5 years old)	<i>n</i> = 1622	<i>n</i> = 428 (26%)	<i>n</i> = 599 (37%)	<i>n</i> = 171 (10.5%)
Gender				
Male	<i>n</i> = 833	218 (26%)	333 (40%)	110 (13%)
Female	<i>n</i> = 789	210 (26%)	266 (34%)	61 (7.5%)
Gestational age				
<37	<i>n</i> = 205	55 (27%)	78 (38%)	19 (9%)
>37	<i>n</i> = 1417	373 (26%)	521 (36.5%)	152 (10.5%)
Maternal prenatal smoking				
No	<i>n</i> = 1333	335 (25%)	468 (35%)	130 (9.5%)
Yes	<i>n</i> = 289	93 (32%)	131 (45%)	41 (14%)
Birthweight for gestational age				
Appropriate (10th–89th%)	<i>n</i> = 1366	369 (27%)	508 (37%)	144 (10.5%)
Small (<10th%)	<i>n</i> = 149	27 (18%)	46 (31%)	15 (10%)
Large (>90th%)	<i>n</i> = 107	32 (30%)	45 (42%)	12 (11%)
Maternal educational level				
<9 years	<i>n</i> = 176	39 (22%)	54 (31%)	20 (11.5%)
9–12 years	<i>n</i> = 539	138 (25.5%)	198 (36.5%)	62 (11.5%)
>12 years	<i>n</i> = 907	251 (28%)	347 (38%)	89 (10%)
Passive smoking at home				
No	<i>n</i> = 1022	260 (25.5%)	366 (36%)	101 (10%)
Yes	<i>n</i> = 600	168 (28%)	233 (39%)	70 (11.5%)
<i>Healthy Growth</i> Study (9–13 years old)	Total cohort population <i>n</i> = 2015	'Yes' for current wheeze <i>n</i> (%) <i>n</i> = 74 (3.5%)	'Yes' for ever wheeze <i>n</i> (%) <i>n</i> = 255 (12.5%)	'Yes' for asthma ever <i>n</i> (%) <i>n</i> = 274 (13.5%)
Gender				
Male	<i>n</i> = 994	49 (5%)	151 (15%)	162 (16%)
Female	<i>n</i> = 1021	25 (2.5%)	104 (10%)	112 (11%)
Gestational age				
<37	<i>n</i> = 379	19 (5%)	55 (14.5%)	59 (15.5%)
>37	<i>n</i> = 1636	55 (3%)	200 (12%)	215 (13%)
Maternal prenatal smoking				
No	<i>n</i> = 1689	56 (3%)	204 (12%)	235 (14%)
Yes	<i>n</i> = 326	18 (5.5%)	51 (15.5%)	39 (12%)
Birthweight for gestational age				
Appropriate (10th–89th%)	<i>n</i> = 1619	54 (3%)	196 (12%)	218 (13.5%)
Small (<10th%)	<i>n</i> = 248	14 (5.5%)	39 (15.5%)	31 (12.5%)
Large (>90th%)	<i>n</i> = 148	6 (4%)	20 (13.5%)	25 (17%)
Maternal educational level				
<9 years	<i>n</i> = 413	11 (2.5%)	43 (10.5%)	52 (12.5%)
9–12 years	<i>n</i> = 805	36 (4.5%)	108 (13.5%)	104 (13%)
>12 years	<i>n</i> = 797	27 (3%)	104 (13%)	118 (15%)
Passive smoking at home				
No	<i>n</i> = 1084	36 (3%)	134 (12%)	151 (14%)
Yes	<i>n</i> = 931	38 (4%)	121 (13%)	123 (13%)

in the models were chosen on the basis of literature reports ascribing asthma-manipulating capabilities to each of them. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) are reported. The Statistical Package for Social Sciences (SPSS), version 20.0 (IBM Corporation, Armonk, NY, USA), was used. A two-tailed P value of < 0.05 was considered statistically significant.

Results

Complete data were collected from 1622 children in the *Genesis* Study and 2015 children in the *Healthy Growth* Study. In the *Genesis* Study, 176 preschoolers were overweight (11%) and 99 were obese (6%); in the *Healthy Growth* Study, 614 preadolescents were overweight (30.5%) and 237 were obese (12%). Descriptive data for both populations are shown in Tables 1 and 2. In the multivariate analysis in preschoolers (Table 3), z -scores of waist/hip circumference, conicity, waist-to-height ratio, skinfold-derived percentage fat mass, biceps, subscapular, suprailiac, and sum skinfold thickness were correlated with asthma ($P = 0.018$ – 0.036). Conversely, BMI z -scores and BMI-defined overweight/obesity were not ($P > 0.05$). Ever wheeze was only associated with suprailiac skinfold thickness ($P = 0.011$).

In the multivariate analysis in preadolescents (Table 4), BMI z -scores, BMI-defined overweight/obesity and z -scores of conicity, waist circumference, waist-to-height ratio, biceps/triceps/subscapular/suprailiac/sum of skinfold thickness, skinfold-derived percentage fat mass, and BIA-derived percentage fat mass were positively associated with physician-diagnosed asthma ($P = 0.006$ – 0.028).

In the *Genesis* Study, BMI z -scores showed a considerable positive correlation with scores of conicity, waist-to-height ratio, and waist/hip circumference, whereas correlation with

sum and discrete skinfolds was weaker (Table 5). In the *Healthy Growth* Study, BMI z -scores were robustly correlated to all other measures of adiposity apart from waist-to-hip ratio (Table 5).

Discussion

In our study, most of the employed anthropometric measurements (including BMI) were positively associated with asthma in children aged 9–13. In contrast, in preschoolers, BMI failed to correlate to asthma; this implies inadequacy of BMI as an adiposity marker in asthma studies in the preschool age.

To date, a link between adult obesity and asthma has been established. However, the nature of a potential correlation remains to be elucidated in children, especially due to difficulties in defining obesity in this period of continuous alterations of body mass (2, 8). BMI normally decreases from age 2 until the age of 5–6 years, reflecting the diminishing subcutaneous fat and increases thereafter; this is termed the ‘adiposity rebound’ (15). Alongside this complex behavior, BMI limitation in discriminating lean from fat mass (7) and the acknowledgment that the same BMI percentile group could be composed of children with wide variations in body fat (16) raise further questions regarding BMI adequacy for pediatric asthma studies. Although a positive BMI/asthma correlation has been postulated in a recent meta-analysis (1), up to 46% discordance between BMI percentiles and central obesity measures in predicting pediatric asthma has recently been reported (8).

Thus, alternative measures of adiposity could be more robustly associated with asthma than BMI, as they likely measure different aspects of fat distribution. Indeed, waist circumference, especially in late childhood, adequately predicts central and visceral adipose tissue (17, 18). Skinfold thickness measurements have also been recommended (19), as they are predictive of total body fat in children and adolescents (15). Accordingly, in our study, waist circumference and skinfold thickness measurements were associated with asthma in both preschoolers and preadolescents; this is highly indicative of an asthma/adiposity correlation in both cohorts, and it circumvents potential confounding by presumed BMI limitations. However, BMI did not fall short in this task in the 9–13 age span and was associated with asthma in preadolescent children. This is in line with BMIs reported suitability for children over 7 years of age (20, 21); however, it is at odds with a report by Mussad et al. (8) in allergic children. Likely explanations could include differences in populations, race, gender (21), and especially age. Indeed, in accord with Mussad et al. in our study, BMI failed to correlate with asthma in the ages of 2–5. Nevertheless, the strong positive association of asthma with the alternative indices in this cohort supports an asthma/adiposity link in this age as well. Consequently, BMI appeared to be unable to unveil this link in preschool children. Accordingly, correlations of BMI with the alternative markers were far stronger in preadolescents ($\rho = 0.73$ – 0.91) than those in preschoolers ($\rho = 0.33$ – 0.72). BMI aside, waist-to-hip ratio – as opposed to waist-to-height

Table 2 Descriptive anthropometric data for both *Genesis* and *Healthy Growth* Study populations. Circumferences are in cm and skinfold thickness in mm

	<i>Genesis</i> Study (2–5 years old)		<i>Healthy</i> <i>Growth</i> Study (9– 13 years old)	
	Mean	SD	Mean	SD
Age	3.62	0.76	11.16	0.66
BMI	16.78	2.02	20.34	3.75
Waist circumference	51.82	4.61	68.81	9.50
Hip circumference	56.03	5.04	84.40	9.26
Waist-to-hip ratio	0.92	0.04	0.81	0.06
Waist-to-height ratio	0.51	0.04	0.46	0.05
Triceps skinfold thickness	9.76	2.90	17.05	5.98
Biceps skinfold thickness	5.95	2.10	10.90	4.83
Suprailiac skinfold thickness	5.72	2.75	14.61	7.35
Subscapular skinfold thickness	6.84	2.38	12.45	6.23
Sum skinfold thickness	28.29	8.73	55.02	22.73
Skinfold-derived% fat mass	17.46	4.72	28.23	7.43

Table 3 Adjusted odds ratios and 95% CI for the association between adiposity indices with parent-reported current/ever wheeze and physician-diagnosed asthma in preschoolers. The covariates of each logistic regression model included one independent anthropometric variable and the confounding variables, that is, prenatal smoking, gestational age, birthweight, gender, parity, breastfeeding, passive smoking at home, nationality, and parental educational level

	Current wheeze	Ever wheeze	Physician-diagnosed asthma
	Odds ratio, 95% confidence interval, and <i>P</i> -value	Odds ratio, 95% confidence interval, and <i>P</i> -value	Odds ratio, 95% confidence interval, and <i>P</i> -value
<i>Genesis Study</i> (2–5 years old)			
BMI-defined overweight vs normal weight	OR = 0.90, CI = 0.62–1.31 <i>P</i> = 0.609	OR = 1.14, CI = 0.81–1.59 <i>P</i> = 0.444	OR = 1.29, CI = 0.78–2.15 <i>P</i> = 0.319
BMI-defined obesity vs normal weight	OR = 1.37, CI = 0.88–2.14 <i>P</i> = 0.158	OR = 1.25, CI = 0.82–1.92 <i>P</i> = 0.293	OR = 1.54, CI = 0.85–2.80 <i>P</i> = 0.149
BMI	OR = 1.06, CI = 0.96–1.16 <i>P</i> = 0.243	OR = 1.06, CI = 0.97–1.16 <i>P</i> = 0.160	OR = 1.10, CI = 0.96–1.27 <i>P</i> = 0.146
Conicity	OR = 1.02, CI = 0.91–1.14 <i>P</i> = 0.719	OR = 1.05, CI = 0.94–1.16 <i>P</i> = 0.357	OR = 1.17, CI = 1.01–1.36 <i>P</i> = 0.036
Waist circumference	OR = 1.01, CI = 0.89–1.13 <i>P</i> = 0.893	OR = 1.04, CI = 0.94–1.16 <i>P</i> = 0.419	OR = 1.21, CI = 1.03–1.42 <i>P</i> = 0.018
Hip circumference	OR = 1.03, CI = 0.91–1.16 <i>P</i> = 0.601	OR = 1.05, CI = 0.94–1.18 <i>P</i> = 0.323	OR = 1.22, CI = 1.03–1.43 <i>P</i> = 0.018
Waist-to-hip ratio	OR = 0.95, CI = 0.84–1.07 <i>P</i> = 0.418	OR = 0.97, CI = 0.87–1.09 <i>P</i> = 0.676	OR = 0.97, CI = 0.81–1.16 <i>P</i> = 0.793
Waist-to-height ratio	OR = 1.08, CI = 0.97–1.21 <i>P</i> = 0.149	OR = 1.05, CI = 0.94–1.16 <i>P</i> = 0.350	OR = 1.20, CI = 1.03–1.40 <i>P</i> = 0.020
Triceps skinfold thickness	OR = 0.97, CI = 0.87–1.09 <i>P</i> = 0.682	OR = 0.98, CI = 0.88–1.09 <i>P</i> = 0.748	OR = 1.12, CI = 0.96–1.30 <i>P</i> = 0.141
Biceps skinfold thickness	OR = 1.02, CI = 0.91–1.14 <i>P</i> = 0.697	OR = 1.06, CI = 0.96–1.18 <i>P</i> = 0.219	OR = 1.17, CI = 1.01–1.36 <i>P</i> = 0.036
Suprailiac skinfold thickness	OR = 1.10, CI = 0.98–1.23 <i>P</i> = 0.090	OR = 1.14, CI = 1.03–1.27 <i>P</i> = 0.011	OR = 1.18, CI = 1.01–1.37 <i>P</i> = 0.033
Subscapular skinfold thickness	OR = 1.07, CI = 0.96–1.20 <i>P</i> = 0.184	OR = 1.03, CI = 0.93–1.14 <i>P</i> = 0.472	OR = 1.18, CI = 1.02–1.36 <i>P</i> = 0.022
Sum skinfold thickness	OR = 1.05, CI = 0.94–1.17 <i>P</i> = 0.392	OR = 1.06, CI = 0.96–1.17 <i>P</i> = 0.234	OR = 1.18, CI = 1.02–1.36 <i>P</i> = 0.022
Skinfold-derived% fat mass	OR = 1.04, CI = 0.89–1.21 <i>P</i> = 0.567	OR = 1.09, CI = 0.95–1.25 <i>P</i> = 0.203	OR = 1.27, CI = 1.04–1.57 <i>P</i> = 0.020

Model adjusted for all confounders, standardized (*z*) scores were used for all continuous variables.

Odd ratios reflect the associations of the dependent with the independent variables for changes in units of standard deviation.

Statistically significant correlations are shown in bold.

ratio – was not associated with asthma in either age, suggesting inadequacy to define adiposity in our cohorts. This was not surprising, as waist-to-hip ratio is contingent upon major gender- and age-specific fluctuations in hip fat mass deposition. Indeed, hip circumference failed to uncover an adiposity/asthma correlation in preadolescents, as opposed to preschoolers, suggesting age dependency. Finally, the lack of consistent association of fat mass with current/ever wheeze may be ascribed to differential perceptions of parents and clinicians about wheeze. Indeed, a considerable variability has been demonstrated, with up to 19% of parents reporting cough where clinicians would instead find ‘wheeze’ (22). Thus, although parents were carefully instructed by trained personnel, misclassification could partially underlie this lack of consistent correlation (22). The variability of wheeze causality can also provide an alternative explanation. Overall,

conicity index, waist circumference, and skinfold thickness were the markers that most consistently uncovered an adiposity/asthma association. However, skinfold thickness measurements are more time-consuming and require special equipment. We therefore favor waist circumference as an obesity marker for asthma-related epidemiology, as it is easy to conduct and has been shown to be a reliable index of central adiposity (17, 18).

Key strengths of our study include a population-based design, investigations in two discrete cohorts of children of different ages, the use of a wide array of markers, and the adjustment for several confounders. We adjusted for low birthweight, short gestational age, maternal prenatal smoking, and secondhand smoke exposure at home, all of which are known asthma risk factors (23–25); we also controlled for breastfeeding, which is believed to protect from asthma (24),

Table 4 Adjusted odds ratios and 95% CI for the association between adiposity indices with parent-reported current/ever wheeze and physician-diagnosed asthma in preadolescent children. The covariates of each logistic regression model included one independent anthropometric variable and the confounding variables, that is, prenatal smoking, gestational age, birthweight, gender, parity, breastfeeding, passive smoking at home, nationality, and parental educational level

	Current wheeze	Ever wheeze	Physician-diagnosed asthma
	Odds ratio, 95% confidence interval, and <i>P</i> -value	Odds ratio, 95% confidence interval, and <i>P</i> -value	Odds ratio, 95% confidence interval, and <i>P</i> -value
<i>Healthy Growth Study</i> (9–13 years old)			
BMI-defined overweight vs normal weight	OR = 1.27, CI = 0.75–2.13 <i>P</i> = 0.365	OR = 1.14, CI = 0.84–1.53 <i>P</i> = 0.390	OR = 1.45, CI = 1.08–1.93 <i>P</i> = 0.012
BMI-defined obesity vs normal weight	OR = 1.31, CI = 0.64–2.66 <i>P</i> = 0.450	OR = 1.34, CI = 0.90–2.01 <i>P</i> = 0.149	OR = 1.69, CI = 1.14–2.50 <i>P</i> = 0.008
BMI	OR = 1.14, CI = 0.93–1.40 <i>P</i> = 0.198	OR = 1.06, CI = 0.95–1.19 <i>P</i> = 0.268	OR = 1.16, CI = 1.04–1.30 <i>P</i> = 0.009
Conicity	OR = 1.13, CI = 0.91–1.41 <i>P</i> = 0.254	OR = 1.11, CI = 0.97–1.26 <i>P</i> = 0.108	OR = 1.17, CI = 1.03–1.33 <i>P</i> = 0.013
Waist circumference	OR = 1.14, CI = 0.91–1.42 <i>P</i> = 0.259	OR = 1.10, CI = 0.96–1.25 <i>P</i> = 0.152	OR = 1.15, CI = 1.01–1.31 <i>P</i> = 0.028
Hip circumference	OR = 1.08, CI = 0.86–1.36 <i>P</i> = 0.497	OR = 1.08, CI = 0.94–1.23 <i>P</i> = 0.247	OR = 1.12, CI = 0.98–1.27 <i>P</i> = 0.086
Waist-to-hip ratio	OR = 1.17, CI = 0.93–1.47 <i>P</i> = 0.181	OR = 1.06, CI = 0.92–1.21 <i>P</i> = 0.400	OR = 1.10, CI = 0.96–1.25 <i>P</i> = 0.158
Waist-to-height ratio	OR = 1.16, CI = 0.93–1.45 <i>P</i> = 0.171	OR = 1.07, CI = 0.94–1.22 <i>P</i> = 0.273	OR = 1.16, CI = 1.02–1.32 <i>P</i> = 0.017
Triceps skinfold thickness	OR = 1.06, CI = 0.85–1.32 <i>P</i> = 0.605	OR = 1.03, CI = 0.90–1.17 <i>P</i> = 0.640	OR = 1.18, CI = 1.04–1.33 <i>P</i> = 0.010
Biceps skinfold thickness	OR = 1.05, CI = 0.84–1.31 <i>P</i> = 0.656	OR = 0.97, CI = 0.85–1.11 <i>P</i> = 0.734	OR = 1.15, CI = 1.01–1.30 <i>P</i> = 0.026
Suprailiac skinfold thickness	OR = 1.11, CI = 0.89–1.39 <i>P</i> = 0.341	OR = 1.06, CI = 0.93–1.21 <i>P</i> = 0.367	OR = 1.17, CI = 1.04–1.33 <i>P</i> = 0.010
Subscapular skinfold thickness	OR = 1.07, CI = 0.86–1.34 <i>P</i> = 0.506	OR = 1.04, CI = 0.91–1.18 <i>P</i> = 0.551	OR = 1.19, CI = 1.05–1.34 <i>P</i> = 0.006
Sum skinfold thickness	OR = 1.08, CI = 0.86–1.35 <i>P</i> = 0.473	OR = 1.03, CI = 0.90–1.18 <i>P</i> = 0.614	OR = 1.19, CI = 1.05–1.35 <i>P</i> = 0.006
Skinfold-derived% fat mass	OR = 1.08, CI = 0.85–1.37 <i>P</i> = 0.501	OR = 1.01, CI = 0.89–1.16 <i>P</i> = 0.814	OR = 1.18, CI = 1.04–1.35 <i>P</i> = 0.011
BIA-derived% fat mass	OR = 1.13, CI = 0.88–1.44 <i>P</i> = 0.322	OR = 1.05, CI = 0.92–1.21 <i>P</i> = 0.428	OR = 1.21, CI = 1.05–1.39 <i>P</i> = 0.006

Model adjusted for all confounders, standardized (*z*) scores were used for all continuous variables.

Odd ratios reflect the associations of the dependent with the independent variables for changes in units of standard deviation.

Statistically significant correlations are shown in bold.

for parity which modifies asthma risk (23), for nationality, and for gender, as boys may have greater proportion of muscle mass. Finally, we adjusted for socioeconomic status (SES) (using parental educational level as a proxy), as children from lower SES backgrounds are more inclined to asthma development possibly due to adverse environmental exposures and lacking medical care (24).

Nevertheless, there are inherent limitations in our study because of its retrospective nature, such as potential misclassification bias. Additionally, asthma is a heterogeneous disease and is therefore prone to misclassification *per se* (5, 26). The cross-sectional design also prohibits inferences about causality. Furthermore, the atopic status of the children could not be assessed. Indeed, atopic children are at a higher

risk of (atopic) asthma and obesity has been reported to perturb primarily in nonatopic asthma mechanics (27). Nevertheless, to date, an adiposity/atopy correlation is yet to be conclusively established. Such an association has been contested (28–30), raising the suggestion that atopy may not be involved in the link between obesity and asthma (albeit there is considerable disparity in the literature (27, 31)). Furthermore, the asthma/obesity link likely derives from a pathogenetic mechanism unrelated to atopy; proposed hypotheses include interference in respiratory function by mechanical effects of obesity or obesity-related systemic inflammation (e.g., adiponectin, IL-6, TNF- α , leptin) (4). We therefore consider it unlikely that atopy could have significantly interfered with our findings. Furthermore, although we did account for

Table 5 Correlation of BMI scores with the alternative adiposity indices in the *Genesis* and *Healthy Growth* studies – Spearman correlation coefficients (rho)

	BMI	
	<i>Genesis</i> Study (2–5 years old)	<i>Healthy</i> <i>Growth</i> Study (9–13 years old)
Spearman correlation coefficient (rho)		
Conicity	0.723	0.915
Waist-to-height ratio	0.665	0.846
Waist circumference	0.595	0.865
Hip circumference	0.561	0.822
Sum skinfold thickness	0.475	0.803
Subscapular skinfold thickness	0.482	0.784
Triceps skinfold thickness	0.423	0.740
Biceps skinfold thickness	0.363	0.736
Suprailiac skinfold thickness	0.329	0.759
Waist-to-hip ratio	0.064	0.351

$P < 0.05$ for all correlations.

nationality in our regression model (Greek vs non-Greek), there were very few non-Caucasian subjects in our cohorts, disallowing reliable adjustment for race; hence, extrapolation of our findings to non-Caucasian populations is risky. Finally, 10–13% of the children bore an asthma diagnosis, a rather high percentage that could be attributed either to parental misreporting or to physician overdiagnosis. The former could be a component of potential recall bias, an inherent limitation of retrospective studies; in regard to the latter, physician diagnosis has been well documented as a robust asthma-identifying epidemiological tool (32). Furthermore, both obese and nonobese adults are likely under the same risk of asthma overdiagnosis (33); this may also apply to children. In fact, asthma may actually be underdiagnosed in obese adolescents as compared to their lean peers (34). In either case, potential overdiagnosis would fail to meaningfully distort the associations in our study.

In conclusion, we uncover a positive correlation of total and regional fat mass indices with pediatric asthma, in both 2- to 5-year-old and 9- to 13-year-old children. This link of asthma with adiposity (as opposed to solely BMI-defined overweight and obesity) was demonstrated in two different cohorts via the use of numerous fat mass markers (including objective measurement through bioelectric impedance). Insofar as weight-manipulating interventions could fulfill a role in

asthma management (35), evidence of an adiposity/asthma link in both preschool and preadolescent children may have important clinical implications. Finally, this is the first study to show that BMI could be efficient as an obesity-defining marker in the context of asthma-related epidemiological studies in preadolescents, but conversely, it may be lacking to that end in preschoolers; this limitation could confound pertinent studies.

Author contributions

George V. Guibas conceptualized, designed, and drafted the manuscript, carried out the statistical analyses and the literature search, and approved the final manuscript; Yannis Manios was in charge of and coordinated both studies, critically revised the manuscript, and approved the final manuscript; Paraskevi Xepapadaki carried out the literature search, contributed to manuscript design, critically revised the manuscript, and approved the final manuscript; George Moschonis coordinated and supervised collection, collation and interpretation of data, contributed to the statistical analyses, critically revised the manuscript, and approved the final manuscript; Nikolaos Douladiris carried out the literature search, critically revised the manuscript, and approved the final manuscript; Christina Mavrogianni collected, collated, and interpreted data, critically revised the manuscript, and approved the final manuscript; and Nikolaos G Papadopoulos contributed to study design, designed, and critically revised the manuscript, and approved the final version as submitted.

Funding statement

The Genesis Study was supported by a research grant from FrieslandCampina Hellas. The Healthy Growth Study received no specific funding.

Conflicts of interest

George Guibas, George Moschonis, Paraskevi Xepapadaki, Nikolaos Douladiris, and Christina Mavrogianni declare no relevant conflict of interest. Yannis Manios has worked as a part-time scientific consultant for FrieslandCampina Hellas. Nikolaos Papadopoulos has received payments for consultancy from ABBOT, Novartis, Menarini; for lectures from MSD, URIACH, GSK, Allergopharma, Stallergenens; for development of educational presentations from MSD, URIACH, MEDA; and grants from Nestle, MSD, Deviblis.

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