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TITLE PAGE

Title: **'Lean' Mass Predicts Asthma Better than Fat Mass among Women**

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This article has an online depository.

ABSTRACT

The obesity phenotype associated with asthma is not known. Our objective was to define the relative contribution of various distributions of fat and lean mass to asthma prevalence.

Data were obtained from 2,525 participants (including 1,422 women) who underwent Dual-energy X-ray Absorptiometry (DEXA) at the year 20 examination in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort. Total, truncal, arm, and leg distributions of fat and lean mass were adjusted to the person's height. Self-reported asthma was the outcome.

Asthma among women was associated with greater total fat mass, arm fat mass, and total lean mass, truncal lean mass, and arm lean mass. Among men, none of the above mass measures were significantly associated with asthma. Among women, the association with asthma was stronger for total lean mass than for total fat mass. Further, among various regional distributions of lean and fat mass in women, truncal lean mass was the strongest predictor.

Total lean mass is more strongly associated than total fat mass with asthma among women. These findings are contrary to the popular perception that excess *physiological* fat drives the obesity-asthma association. Rather, we hypothesize that ectopic fat within the 'lean' tissues drives this association among women.

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Keywords:

Asthma

Dual energy X-ray absorptiometry.

Fat mass

Lean mass

Abbreviations:

DEXA: Dual energy X-ray absorptiometry

CARDIA: Coronary Artery Risk Development in Young Adults

BMI: Body mass index

OR: Odds ratio

SD: Standard deviation

MAIN TEXT

Introduction:

Obesity is a risk factor for asthma, particularly among women [1-3]. The mechanistic basis for the association between obesity and asthma is unknown and was considered a research priority at a United States National Heart Lung and Blood Institutes workshop [3]. A major limitation of the obesity-asthma literature is that it has focused on Body Mass Index (BMI) to define obesity. It is now known that a large value for BMI is in fact a collection of various phenotypes, some but not all relating to adiposity. It is unclear whether asthma is associated with a specific phenotype of obesity.

Various distributions of fat and skeletal muscle (such as in the trunk, arm and leg) may have varying mechanical and inflammatory properties and consequently health-related effects. For instance, truncal fat may carry a higher risk than arm or leg fat for diseases that constitute the Metabolic Syndrome [4]. In fact, leg fat, may be 'metabolically protective' and may mitigate insulin resistance [5]. Further, truncal fat may have greater mechanical impact on forced vital capacity than arm or leg fat, an effect that may be important in asthma pathogenesis [6]. Truncal fat itself is a collection of fat compartments with varying metabolic activity, including visceral, deep abdominal wall subcutaneous, and superficial abdominal wall subcutaneous fat. Among the various components of truncal fat, visceral fat is the most strongly correlated with features of the Metabolic Syndrome [4]. While visceral fat may be a relatively more important source of adiponectin [7], abdominal subcutaneous fat may be a relatively more important source of leptin

[8] – adipokines with opposing associations with asthma [1, 9]. Furthermore, it has become increasingly apparent that intramuscular fat is strongly associated with insulin resistance [10] and low serum adiponectin concentrations [11], although its relationship with asthma is not known. The objective of this study was to define the relative contributions of various distributions of fat and lean mass to asthma prevalence in men and women separately. Since this is the first study in the literature to evaluate the various distributions of fat and lean mass in relation to asthma, we chose a cross-sectional study design.

Methods

Study Design

This was a cross-sectional data analysis from the Year 20 examination of the prospective Coronary Artery Risk Development in Young Adults (CARDIA) cohort. During 1985-1986, CARDIA randomly recruited 5,115 black and white men and women, aged 18 to 30 years, from the general population of Birmingham, Alabama; Chicago, Illinois; and Minneapolis, Minnesota and from the membership of the Oakland Kaiser-Permanente Health Plan in Oakland, California. Follow-up examinations were completed 2, 5, 7, 10, 15, and 20 years later. Detailed methods, instruments, and quality control procedures are described at the CARDIA website (http://www.cardia.dopm.uab.edu/ex_mt.htm) and in other published reports [12, 13]. Retention of CARDIA participants has been excellent as 3,549 persons were examined at year 20 examination, constituting 72% of the survivors from the baseline cohort. Of those examined at year 20, 2,705 participants (76.2%) underwent Dual-energy X-ray Absorptiometry (DEXA)

examination. After excluding those with *former* asthma (n = 180) at year 20, data on 2,525 participants were analyzed. Participants with former asthma were excluded in the primary analysis to obtain the greatest discrimination between those with current asthma and without asthma. Alternate analyses were performed by separately combining participants with former asthma with either of the two groups with current or never asthma. Self-reported information was obtained from all participants using standardized questionnaires. Height and weight were measured by certified technicians using standardized equipment with participants wearing light clothing, and no shoes.

Dual-energy X-ray Absorptiometry (DEXA)

DEXA (Hologic QDR 4500) was used to determine fat mass and lean mass (*i.e.* non-fat and non-bone soft tissue content) for the whole body and its regions (*i.e.* trunk, arms, and legs). DEXA-assessed lean mass primarily comprises of skeletal muscle and visceral mass but includes fat deposits present within and around muscle and viscera. Analogous to the commonly used body mass index (BMI), all DEXA-assessed mass measures were adjusted for the person's height [14]. Additional details about DEXA measurements and quality control are provided in the online depository. As discussed in the depository, we noted no evidence of selection bias on the obesity-asthma association with respect to DEXA measurement at year 20 examination.

Outcome

Participants with self-reported current asthma were compared to those without asthma. Current asthma was defined as participant self-report of healthcare provider-diagnosed asthma at any time PLUS either presence of current asthma symptoms during the previous twelve-months or a

validated participant report of current use of asthma medication/s. This definition is more stringent than in most epidemiological studies where provider diagnosis is the sole criterion for defining asthma [15]. Validation of medication use was performed whenever possible by direct examination of the medication containers by study personnel. Those who never reported having asthma or taking asthma medications at any of the examinations were included in the referent group. Former asthma was similarly defined as participant self-report of provider-diagnosed asthma at any time PLUS absence of both current asthma symptoms during the previous twelve-months and current use of asthma medication/s.

Covariates

All multivariate models include the following covariates - self-reported smoking status, race (blacks *vs.* whites), age, study center at which the DEXA was performed, and physical activity – all measured at year 20 examination. Smoking status was treated as a categorical variable, comprising current, former, and never smokers. The frequency of participation in a range of specific heavy and moderate intensity physical activities in the previous year was obtained from a validated questionnaire [16]. Data were converted into a weighted physical activity score (in exercise units), using the methods used by Folsom *et al* [17]. The score was logarithmically transformed because of its non-normal distribution.

Statistical analysis

Tertiles of predictor variables were studied *s*ince several variables were not normally distributed, despite logarithmic transformation. Multivariable logistic regression analyses were used in men and women separately (since our previous studies had demonstrated the obesity-asthma

association only in women) [1, 2]. The effect of total lean and fat mass measures on asthma was separately studied after adjusting for covariates, presented as minimally adjusted models. Each mass measure was then adjusted for the other, presented as a full model, to obtain the stronger predictor. Similar analyses for additional components of fat and lean mass were performed, as discussed in the online depository. Multiplicative interactions of sex on the associations between various predictor measures and asthma status were also studied. A two-sided p-value of < 0.05 was considered statistically significant for all tests. All statistical analyses were done using the Statistical Analysis Software (SAS) package version 9.1 (Cary, NC). All subjects gave informed consent for their participation in the study. This study was approved by the Institutional Review Boards at University of New Mexico, Albuquerque, NM and at each of the CARDIA study sites.

Results:

Participant Characteristics

Data on 2,525 subjects (1,103 men and 1,422 women) were analyzed. Almost twice as many women (146 or 10.3%) as men (59 or 5.3%) had asthma. As expected, men had greater lean mass and lesser fat mass than women in all regions of the body ($p < 0.001$, Table I). For every unit of total fat mass, men had approximately twice as much total lean mass as women. A greater proportion of fat mass was distributed in the trunk in men, as compared to women.

Table 1: Distribution of selected characteristics among men and women, according to asthma status; CARDIA calendar year 20.

Characteristic	Men			Women		
	Asthma present (n=59)	Asthma absent (n =1,044)	p value	Asthma present (n=146)	Asthma absent (n = 1,276)	p value
DEMOGRAPHIC CHARACTERISTICS						
Age (years)	44.9 ± 3.6	45.2 ± 3.5	0.56	45.2 ± 3.7	45.2 ± 3.7	0.85
Race (% blacks)	32.2	40.6	0.20	57.5	45.9	0.008
Low annual household income (%, < $25,000)	17.2	11.9	0.23	20.7	15.8	0.13
Physical Activity (Exercise units)[3]	343.8 (67.6, 1749.0)	292.9 (36.7, 2339.3)	0.15	165.7 (8.8, 2495.9)	172.4 (11.8, 2528.0)	0.21
Current Smoking (%)	17.0	20.7	0.63	24.7	15.4	0.01
Presence of Hay fever (%)[2]	57.6	28.5	<0.001	44.5	28.4	<0.001
Body Mass Index (BMI)[1]	27.6 ± 4.2	28.3 ± 5.7	0.17	31.0 ± 7.1	28.9 ± 7.0	< 0.001
FAT MASS INDICES						
Total Fat Mass[1]	6.4 ± 2.8	6.6 ± 2.7	0.42	11.7 ± 4.6	10.4 ± 4.5	0.001
Truncal Fat Mass[1]	3.2 ± 1.5	3.4 ± 1.5	0.48	5.2 ± 2.2	4.6 ± 2.3	0.002
Arm Fat Mass[1]	0.8 ± 0.5	0.8 ± 0.4	0.67	1.8 ± 1.1	1.5 ± 1.0	0.003
Leg Fat Mass[1]	2.0 ± 0.9	2.1 ± 0.9	0.33	4.3 ± 1.7	4.0 ± 1.6	0.02
LEAN MASS INDICES						
Total Lean Mass[1]	20.1 ± 2.2	20.7 ± 3.7	0.22	18.2 ± 2.7	17.3 ± 2.7	<0.001
Truncal Lean Mass[1]	9.7 ± 1.2	9.9 ± 1.8	0.47	8.9 ± 1.3	8.5 ± 1.3	<0.001
Arm Lean Mass[1]	2.6 ± 0.4	2.7 ± 0.6	0.25	1.9 ± 0.4	1.8 ± 0.4	<0.001
Leg Lean Mass[1]	6.6 ± 0.9	6.8 ± 1.2	0.31	6.0 ± 1.1	5.8 ± 1.1	0.004

Note 1: Analogous to the commonly used body mass index, all DEXA-assessed mass measures were adjusted to the height of the person - by dividing the mass (in kilograms) by the square of height (in meters). The difference between total and sum of the above components of fat and lean mass was due to the head measures. Additionally, tertiles of BMI (<25.5, 25.5-30.2, and ≥ 30.3 kg/m^2) corresponded well to the standard definitions of normal weight, overweight and obese.
Note 2: All variables were measured at CARDIA year 20 examination except for the presence of hay fever (which was assessed at year 0 examination on 1,098 men and 1,419 women).
Note 3: All continuous data are presented as mean ± S.D. except physical activity that is presented as geometric mean (95% C.I.). Chi-square and t-tests were used as appropriate.

Fat and Lean Mass Measures Associated with Asthma

In bivariate analyses (Table 1), women with asthma had greater fat and lean mass than women without asthma, irrespective of the region of distribution ($p \leq 0.02$ for all analyses). Interestingly,

men with asthma had lower mass measures than men without asthma, but these differences were not significant.

In multivariable analyses, total fat mass and arm fat mass were both positively associated with asthma among women ($p \leq 0.02$ for both analyses; weak sex interactions with $p \leq 0.13$ for both analyses, Table 2). Surprisingly, truncal fat mass was not significantly associated with asthma in either sex in the multivariable analysis. Total lean mass, truncal lean mass, and arm lean mass were positively associated with asthma in women ($p \leq 0.004$ for all analyses; sex interactions with $p \leq 0.11$ for all analyses). Neither fat nor lean mass measures were significantly associated with asthma among men.

Table 2: Multivariable analyses of the associations of asthma with tertiles of various obesity measures; CARDIA calendar year 20.

Tertiles of Mass Measures	Men n = 1,103 O.R. (95% C.I.)	p value	Women n = 1,422 O.R. (95% C.I.)	p value	Mass measure-by-sex multiplicative interaction p value (n = 2,525)
Total Body Mass (BMI)	1.0	0.39	1.0	0.006	**0.01**
	0.87 (0.47, 1.58)		1.48 (0.91, 2.43)		
	0.60 (0.28, 1.25)		2.10 (1.33, 3.30)		
FAT MASS INDICES					
Total Fat Mass	1.0	0.47	1.0	0.01	0.13
	0.69 (0.38, 1.25)		1.40 (0.76, 2.59)		
	0.92 (0.39, 2.17)		2.13 (1.21, 3.78)		
Truncal Fat Mass	1.0	0.38	1.0	0.07	0.13
	0.67 (0.37, 1.21)		1.27 (0.75, 2.16)		
	0.74 (0.35, 1.58)		1.71 (1.05, 2.76)		
Arm Fat Mass	1.0	0.86	1.0	0.02	0.08
	0.97 (0.55, 1.70)		1.80 (0.92, 3.50)		
	0.74 (0.25, 2.19)		2.46 (1.30, 4.66)		
Leg Fat Mass	1.0	0.85	1.0	0.07	0.75
	0.85 (0.46, 1.58)		1.04 (0.50, 2.15)		
	1.11 (0.38, 3.28)		1.60 (0.80, 3.20)		

LEAN MASS INDICES					
Total Lean mass	1.0	0.15	1.0	<0.001	**0.005**
	0.49 (0.21, 1.15)		2.07 (1.37, 3.12)		
	0.43 (0.19, 1.01)		2.18 (1.33, 3.55)		
Truncal Lean Mass	1.0	0.52	1.0	<0.001	0.11
	1.11 (0.44, 2.81)		1.72 (1.14,2.59)		
	0.80 (0.32, 2.03)		2.32 (1.48, 3.64)		
Arm Lean Mass	1.0	0.07	1.0	0.004	**0.003**
	0.26 (0.08, 0.86)		1.87 (1.26, 2.80)		
	0.27 (0.08, 0.86)		2.23 (1.18, 4.21)		
Leg Lean Mass	1.0	0.44	1.0	0.07	0.17
	0.62 (0.27, 1.40)		1.61 (1.07, 2.41)		
	0.60 (0.26, 1.37)		1.27 (0.77, 2.09)		

Note 1: All analyses were adjusted for age, race, clinical center, smoking status, and log-transformed physical activity score.
Note 2: All mass measures were height-adjusted by dividing the mass (in kilograms) by the square of height (in meters).
Note 3: Lowest tertile for each measure was used as referent value.
Note 4: All variables in the table were measured at CARDIA year 20 examination.
Note 5: Similar results were obtained after additional adjustment for atopic status (as evidenced by self-reported hay fever) at baseline (year 0) examination.

Relative Contributions of Fat and Lean Mass Measures towards Asthma

To better understand the relative contributions of fat and lean mass measures towards the odds for asthma, we first performed correlational analysis between corresponding fat and lean mass measures (Table 3). The overall correlations were stronger among women than men. However, formal tests of collinearity suggested that the corresponding fat and lean mass variables were not collinear. Further, in order to quantify the relative contributions of total fat mass and total lean mass to the odds for asthma among women, we performed multivariable logistic regression analyses (Table 4). In the minimally adjusted models, total lean mass was found to be a slightly stronger predictor of asthma among women than total fat mass. Adjusting total lean mass for total fat mass (in the full model) did not eliminate the association of total lean mass with asthma among women. On the other hand, adjusting total fat mass for total lean mass reduced the

association of total fat mass with asthma among women to a non-significant level. This suggests that lean mass is a stronger predictor for asthma among women than fat mass and that the lean mass-asthma association is not confounded by fat mass.

Table 3: Correlation coefficients between DEXA-assessed fat and lean mass measures in men and women; CARDIA calendar year 20.

Fat and Lean Mass Components	Men	Women
	All (n=1,103)	All (n= 1,422)
Total Fat *v.* Total Lean Mass	0.52	0.77
Truncal Fat *v.* Truncal Lean Mass	0.53	0.73
Arm Fat *v.* Arm Lean Mass	0.38	0.67
Leg Fat *v.* Leg Lean Mass	0.53	0.72

Note 1: All variables were measured at CARDIA year 20 examination.
Note 2: BMI tertile cut points used in this analysis were <25.5, 25.5-30.2, and ≥ 30.3 kg/m^2.
Note 3: The p values for all correlation coefficients in the table were < 0.001.
Note 4: An expanded table is provided in the online depository Table E2.

Table 4: Multivariable analysis showing a stronger association of total lean mass than total fat mass on asthma in women; CARDIA calendar year 20.

Fat and Lean Mass Component	Minimally adjusted model		Full model	
	OR for third tertile *vs.* first tertile (95% CI)	Overall p value	OR for third tertile *vs.* first tertile (95% CI)	Overall p value

Total Lean Mass	2.18 (1.33, 3.55)	<0.001	1.87 (1.04, 3.36)	0.03
Total Fat Mass	2.13 (1.21, 3.78)	0.01	1.46 (0.77, 2.77)	0.52

Note 1: To assess the relative strength of the associations of both total fat and lean mass on asthma, we show the effect of each of our two measures in separate logistic regression analyses in the minimally adjusted model and each of their effect after adjustment for the other measure in the full model. In addition, both minimally-adjusted and full models were adjusted for covariates - age, race, clinical center, smoking status, and log-transformed physical activity score.
Note 2: All variables were measured at CARDIA year 20 examination.
Note 3: Similar results were obtained after additional adjustment for atopic status (as evidenced by self-reported hay fever) at baseline (year 0) examination.

We further analyzed the relative contribution of the various distributions of fat and lean mass towards the odds for asthma in women in Table 5. Among various measures of lean and fat mass studied, truncal lean mass and arm fat mass were found to be the strongest predictors of asthma respectively among women in the minimally-adjusted models. After full adjustment, truncal lean mass remained a strong predictor of asthma among women but arm fat mass did not. On the other hand, leg lean mass was *inversely* associated with asthma among women. Truncal fat mass was however, not associated with asthma among women.

Table 5: Multivariable analysis of six lean and fat mass components showing that truncal lean mass has the strongest positive association with asthma among women (n = 1,422); CARDIA calendar year 20.

Fat and Lean Mass Components	**Minimally-adjusted model**		**Full model**	
	OR for the third tertile only (95% CI)	Overall p value	OR for the third tertile only (95% CI)	Overall p value
Truncal Fat Mass	1.71 (1.05, 2.76)	0.07	0.66 (0.29, 1.49)	0.58
Arm Fat Mass	2.46 (1.30, 4.66)	0.02	2.51 (0.86, 7.31)	0.17
Leg Fat Mass	1.60 (0.80, 3.20)	0.07	0.83 (0.31, 2.21)	0.41

Truncal Lean Mass	**2.32 (1.48, 3.64)**	**<0.001**	**2.81 (1.39, 5.69)**	**0.02**
Arm Lean Mass	2.23 (1.18, 4.21)	0.004	1.79 (0.82, 3.91)	0.22
Leg Lean Mass	1.27 (0.77, 2.09)	0.07	0.40 (0.19, 0.84)	0.02

Note 1: To assess the relative strength of association of various components of fat and lean mass on asthma, we show the effect of each component in separate logistic regression analyses in the minimally adjusted model and each of their effect after adjustment for all other components in the full model. Each row presents the third tertile compared to the first. In addition, both minimally-adjusted and full models were adjusted for covariates - age, race, clinical center, smoking status, and log-transformed physical activity score.
Note 2: All variables were measured at CARDIA year 20 examination.
Note 3: Similar results were obtained after additional adjustment for atopic status (as evidenced by self-reported hay fever) at baseline (year 0) examination.

Alternate Analytic Strategies

Alternate analytic strategies are discussed in the online depository and show no effect of atopy, menopause, and race on the above-described associations. We reanalyzed the data by including participants with former asthma among either of the two groups with current asthma and never asthma and obtained similar results. Principal components analysis was performed and showed that no combination of regional fat and lean mass measures was superior to truncal lean mass alone in predicting asthma in women.

Discussion:

We found that increased total 'lean' mass was associated with higher odds for asthma only among women in this cross-sectional analysis nested within the prospective CARDIA study. This association was stronger than the association of total fat mass with asthma among women. Among all the regional fat and lean mass measures, truncal lean mass was the strongest

predictor. On the other hand, neither fat nor lean mass measures were associated with asthma among men. These findings are contrary to the popular perception that excess *physiological* fat drives the obesity-asthma association in women.

Why might greater lean mass be associated with *higher* odds for asthma among women? DEXA-assessed 'lean' mass is not entirely fat-free but includes the smaller and highly metabolically active ectopic fat within the skeletal muscle and viscera. Sutherland *et al.* in their study of lung function suggested that while lean mass was a measure of muscle bulk in men, excess lean mass in women was a measure of obesity [18]. It is therefore possible that excess ectopic fat may explain our findings in obese women.

Intramuscular fat infiltration, also described in lay terms as 'marbling of muscle', is more pronounced in women than men, independent of overall obesity [19, 20]. Consistent with these observations, our data demonstrate that positive correlations between lean mass and fat mass measures are stronger among obese women than obese men (Table 3). Further, intramuscular fat is associated with high systemic leptin and low systemic adiponectin concentrations (11, 21-24) and increased expression of tumor necrosis factor –alpha [21] – changes possibly associated with asthma [1, 9, 22].

Additionally, truncal lean mass includes visceral fat components that may be associated with asthma. Visceral fat, constituting only about 10% of total fat, surrounds and infiltrates internal organs in the intrathoracic, intraabdominal, and intrapelvic compartments. Our study is unable to answer if a specific component of visceral fat (such as epicardial or hepatic fat) drives the

obesity-asthma association in women. Nevertheless, pro-inflammatory adipokines expressed by visceral fat components may have direct access to portal and systemic circulation [23], accounting for the disproportionately greater inflammatory effect of visceral fat relative to its small size. Further, like intramuscular fat, visceral fat may be associated with high systemic leptin and tumor necrosis factor-alpha and low systemic adiponectin concentrations [24-28] - changes again possibly associated with asthma [1, 9, 22]. Further, truncal mass (of which there is disproportionate lean than fat mass) may have direct mechanical effects on diaphragmatic position and movement and chest wall recoil that may increase airway responsiveness [29].

Unlike truncal lean mass that was positively associated with asthma among women, we report that leg lean mass was *inversely* associated with asthma among women. One possible explanation is that skeletal muscle in different regions may have different metabolic and inflammatory effects [30]. However, the bases for these differences remain unknown.

Our study also suggests that lean mass may be a *better* predictor than fat mass for asthma among women. A plausible explanation is that the smaller ectopic fat depots (components of DEXA-assessed lean mass) may be more important from the inflammatory standpoint than the larger, physiological fat depots.

Further, why might arm fat (which constitutes approximately 13% of total fat) be a *better* predictor for asthma among women than other larger fat compartments in the body (Table 5 and online depository Table E3)? Arm fat may have a different metabolic profile compared to either truncal fat or leg fat [31]. Relative to other fat compartments, leg fat may *enhance* serum

adiponectin concentrations and be ‘metabolically benign’ [31]. On the other hand, truncal fat is not a uniform compartment but includes two subcomponents with varying metabolic activity - superficial abdominal subcutaneous fat that is ‘metabolically benign’ and deep abdominal subcutaneous fat that is metabolically active (quite like visceral fat) [32]. However, since DEXA can’t separate these two subcomponents, the net effect of truncal fat mass on asthma in women may be neutralized.

We also note a sexual dimorphism of specific lean mass measures with respect to asthma since the odds ratios are directed oppositely in men and women. This is not due to the smaller height in women, since height-adjusted mass indices were used for these analyses. Possible explanations include the effect of sex hormones, gonadotrophic hormones, or sex hormone binding globulin; sex-specific effects of adipokines; and sex-specific differences in adiponectin isoform distribution and intramuscular lipid deposition.

Finally, participants with asthma at CARDIA year 20 examination were mostly of intermittent or mild persistent severity. Thus, systemic steroid intake for the treatment of asthma was reported by only two participants at that examination, both being men. We, therefore, do not think our findings can be explained by the effect of systemic steroids on the repartition of fat and lean tissues.

The strengths of our study include its sex-specific stratified analysis, well-defined study population set within a cohort structure, adjustment for physical activity, and use of DEXA data to assess regional body composition. Instead of using absolute mass obtained from DEXA, we

have adjusted all mass measures for height which may allow for better comparison of individuals of different sizes [33]. Further, the study results generate innovative hypotheses regarding the mechanistic basis for the obesity-asthma association.

Nevertheless, DEXA itself has some limitations. Current DEXA software assumes a constant water content of lean mass but whether this is true in fluid overloaded obese populations is unknown. DEXA inaccurately assesses ectopic fat as lean mass. Its accuracy in the obese may also be adversely affected by the effect of increased body thickness on 'beam hardening' and increased body size falling outside the scan range or scanner weight limit. Although whole-body region DEXA strongly correlates with site-specific DEXA, the measurement may provide somewhat different estimates. Several limitations of DEXA may be overcome in future studies of the role of lipid content of skeletal muscle and viscera in asthma by using computerized tomography, magnetic resonance spectroscopy, or histopathological techniques.

The study has some additional limitations as well. Atopic status was measured not at year 20 but at year 0 examinations, using self-report. The results of this study may not be generalizable to populations other than blacks and whites. This study will not be able to evaluate objectively-defined asthma phenotypes. Self-reported asthma definitions are well accepted in epidemiological literature but may result in misclassification bias [15, 34]. However, this bias is likely to be non-differential between obese and non-obese populations [34]. Non-differential misclassification biases the estimate of association towards the null value and is unlikely to produce a spurious effect [15]. Finally, this is an observational cross sectional study which allows for hypothesis generation but does not prove causality or the direction of association.

However, prior prospective studies have suggested that obesity precedes asthma and not *vice versa* [15].

Our findings that increased total lean mass is more strongly associated with asthma than fat mass among women are contrary to the popular perception that excess physiological fat drives the obesity-asthma association. Rather, we hypothesize that ectopic fat within the 'lean' tissues drives this association among women. Our cross-sectional results do allow for innovative hypothesis generation in the field of obesity and asthma. However, our hypotheses would need further confirmation with longitudinal study designs and/or use of more sophisticated techniques of measuring ectopic fat such as computed tomography and magnetic resonance spectroscopy. If true, decreasing ectopic fat mass and not simply increasing the fat-free lean mass or decreasing physiological fat mass would be a reasonable goal in the prevention and treatment of asthma among obese women.

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