

Leptin Is Inversely Associated With Lung Function in African Americans, Independent of Adiposity: The Jackson Heart Study

DeMarc A. Hickson^{1,2}, Cecil M. Burchfiel³, Marcy F. Petrini⁴, Jiankang Liu²,
Brenda W. Campbell-Jenkins¹, Rajesh Bhagat^{4,5} and Gailen D. Marshall²

Leptin, a 16-kDa protein, has proinflammatory properties and has been linked to respiratory physiological responses in majority white populations. Little is known, however, about the relationship of leptin with lung function in nonwhites. Cross-sectional associations of circulating serum leptin concentrations with forced expiratory volume in 1 s (FEV₁), FEV in 6 s (FEV₆), and vital capacity (FVC), assessed by spirometry, were examined in 4,679 African-American men and women participants (54.3 ± 12.4 years; 62.7% women) in the Jackson Heart Study (JHS). The independent association of leptin was examined in relation to FEV₁, FEV₆, and FVC% predicted after adjustment for age, education, smoking status, pack-years of cigarette smoking, respiratory medication use, and menopausal status in women; additional adjustment included total body weight, waist circumference, and BMI. Serum leptin was inversely related to FEV₁, FEV₆, and FVC% predicted values in men. A dose–response relationship was observed with men in the highest leptin quartile having a significantly lower lung function compared to men in the lower leptin quartile. BMI significantly modified this relationship in women: leptin was most consistently associated with lung function in obese women, less consistent in overweight women, and absent in normal-weight women. Serum leptin concentration was strongly, inversely, and independently associated with lung function in African Americans, especially African-American men and obese women.

Obesity (2011) **19**, 1054–1061. doi:10.1038/oby.2010.240

INTRODUCTION

Reduced lung function is a significant predictor of mortality (1–5), cardiovascular disease risk factors (6), including type 2 diabetes (7,8), hypertension, (8,9) and cardiac hypertrophy (9), and coronary heart disease (10). African Americans experience greater cardiovascular mortality and related clinical outcomes (11) along with having considerable differences in lung capacity and dynamics (12) than whites. Low lung function may contribute to disparities in cardiovascular disease among African Americans. Important questions remain, however, regarding the main risk factors for reduced lung function, especially in African Americans.

The association of obesity with adverse cardiovascular outcomes and higher prevalence of cardiovascular risk factors, including reduced lung function, is well recognized (13–17). Forced expiratory volume in 1 s (FEV₁) and vital capacity (FVC) have been shown to decrease with increasing abdominal obesity (15–17), including among normal-weight subjects

(16), even after controlling for BMI. Leptin, an adipocyte-derived signaling factor (18–20), is a 16-kDa protein product of the obesity (*ob*) gene that is produced by adipose tissue and increases in accordance to body fat and weight (18,21). Leptin circulates to the brain and interacts with receptors in the hypothalamus to regulate appetite (22). Leptin receptors are also expressed in normal lung tissue and SQ-5 cells (23,24). Studies have demonstrated that leptin is a respiratory stimulant (24,25) and modulates lung development (26). In animal models, leptin has been shown to be necessary for early postnatal lung development and parenchymal remodeling and is associated with enlarged alveolar surface area (26). Leptin indirectly affects lung diseases through its effects on sympathetic outflow and immune modulation (27,28). Thus, animal (and human) models suggest that leptin affects both the structure and function of the respiratory system.

Hyperleptinemia has been linked to poor cardiovascular and respiratory conditions, including reduced lung function,

¹Jackson State University, Jackson Heart Study, Jackson, Mississippi, USA; ²University of Mississippi Medical Center, Department of Medicine, Jackson, Mississippi, USA; ³National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Health Effects Laboratory Division, Morgantown, West Virginia, USA; ⁴University of Mississippi Medical Center, Division of Pulmonary, Critical Care & Sleep Medicine, Jackson, Mississippi, USA; ⁵Sonny Montgomery Veterans Affairs Hospital, Jackson, Mississippi, USA. Correspondence: DeMarc A. Hickson (demarc.a.hickson@jsums.edu)

Received 17 February 2010; accepted 3 September 2010; published online 21 October 2010. doi:10.1038/oby.2010.240

asthma, and chronic obstructive pulmonary disease, even after adjusting for adiposity (29–40). Few studies, however, have investigated the associations of serum leptin with lung function. Although three studies of which we are aware have examined the associations of serum leptin with FEV₁ and FVC, sample sizes were small (36,39), methodological approaches have been inconsistent (39,40), and results have been inconclusive (39). To our knowledge, no large population-based studies have investigated the associations of serum leptin with lung function in large population samples of African Americans. Determining whether serum leptin is an important risk factor for reduced lung function could yield important insights into differences in lung function between African Americans and whites and reasons for racial disparities in respiratory conditions.

The objective of this study was to investigate the associations of serum leptin with spirometry measures of lung function in a population-based cohort of middle-aged and elderly African-American adults. We used spirometry data from the baseline examination (2000–2004) of the Jackson Heart Study (JHS) to examine the hypothesis that higher serum leptin level was associated with reduced lung function.

METHODS AND PROCEDURES

The JHS is a large, population-based observational study to investigate the etiology of cardiovascular, renal, and respiratory diseases in African Americans residing in a three-county metropolitan area in central Mississippi (41). Noninstitutionalized African Americans between the ages of 35 and 84 years were recruited from households in 102 US Census tracts (42); eligible family members ≥ 21 years were enumerated and recruited for participation (43). Nearly one-third of the cohort comprised Atherosclerosis Risk in Communities study participants from the Jackson, Mississippi site. Other cohort members consisted of volunteer (30%) and randomly selected (17%) residents. A total of 5,301 participants underwent extensive clinical examinations, including pulmonary function tests, provided blood specimens, and provided a history of medical and health conditions. Informed consent was received from all participants and institutional review board approval was obtained from the three participating JHS institutions.

In total, 5,011 (94.5%) JHS participants performed spirometry between September 2000 and March 2004. Of the 4,976 (93.9%) participants whose spirometry met American Thoracic Society recommendations for equipment performance, acceptability of each maneuver, and test repeatability (44), 4,848 had all anthropometric measurements and 4,832 had clinically acceptable leptin values. Participants who were >80 years of age ($n = 30$) were excluded because the spirometric reference equations developed by Hankinson *et al.* (12) were based on healthy African-American men (≥ 20 years) and women (≥ 18 years) ≤ 80 years. Of these 4,802 participants, 4,679 had a BMI ≥ 18.5 kg/m² and had a complete covariate profile.

Pulmonary function

Computerized spirometry was measured with a dry rolling seal spirometer (Occupational Marketing, Houston, TX) and performed between 0700 and 1200 hours in the JHS Pulmonary Function Lab (45). Participants were instructed through demonstration by certified pulmonary function technicians in the proper procedure using nose clips: complete inhalation, placement of the mouthpiece between teeth, tight seal with lips, and blasting initial exhalation followed by a non-forced exhalation after the first 3 s. Participants performed up to eight maneuvers or until three acceptable and two repeatable maneuvers were achieved. The maximum FEV₁, FEV₆, and FVC value from the acceptable maneuvers was used in this analysis. To adjust for age and height,

we used published race- and sex-specific prediction equations for FEV₁, FEV₆, and FVC derived from the National Health and Nutrition Examination Study III (NHANES) population (12).

Serum leptin concentrations

Early morning fasting blood samples were collected by certified phlebotomists and centrifuged at the local laboratory using a Cobras centrifuge analyzer (Hoffmann-La Roche). Serum leptin concentrations were measured using a Sensitive Human Leptin Radioimmunoassay kit (LINCO Research, St Charles, MI) of I-labeled Human leptin and a Sensitive Human Leptin antiserum against highly purified recombinant human leptin. The intra- and interassay coefficients of variation were $<5\%$. The analytic limit of detection was 0.5 ng/ml.

Anthropometric measures

Participants were instructed to dress in a light-weight examination gown and to remove their shoes and any constricting undergarments. Standing height and weight were measured using standard procedures. BMI was calculated as weight divided by height (kg/m²). Waist circumference was measured at the umbilicus using an anthropometric tape and rounded to the nearest centimeter.

Covariates

Age, sex, education, smoking status, pack-years of cigarette smoking, respiratory medication use, and menopause status in women were included in this analysis. Education was classified as less than a high-school diploma and high-school diploma and above and smoking status was classified as current, former, and never smoker. For former and current smokers, pack-years of cigarette smoking was calculated as the number of years of smoking times the average number of cigarettes smoked per day divided by 20. Respiratory medication use was based on the use of respiratory medications within 2 weeks of the clinic visit and details have been reported elsewhere (46). Postmenopausal status was considered present for women who had not experienced a menstrual period or bleeding within the last 2 years or for those who reported having reached menopause or the change of life.

Statistical analysis

Selected baseline characteristics were compared across quartiles of increasing leptin values; *P* values for linear trend were calculated by including leptin as an ordinal predictor in the model. Leptin values were positively skewed, so values were log transformed. Age-adjusted Spearman correlation coefficients were computed to assess the association between leptin and anthropometric measures. Multivariable linear regression models were utilized to examine the independent relationships between leptin and lung function. Models were generated in stages: model 1 adjusted for age, education, smoking status, pack-years of cigarette smoking, respiratory medication use, and menopausal status in women and model 2 further adjusted for adiposity (fully adjusted model). We controlled for total body weight, waist circumference, and BMI to reduce potential confounding. Adjusted least-square mean lung function values were computed across the gradient of leptin quartiles. Although no correction for multiple comparisons was made, linear trends in mean lung function values were examined. All analyses were stratified by sex because prior work demonstrated heterogeneity in the association of leptin with asthma by sex (37). In addition, leptin concentrations have been shown to differ substantially by sex, with women having greater leptin concentrations than men (47). Interactions between different variables were investigated in age-adjusted models. The SAS statistical software (Cary, NC) was used to conduct all analyses. All tests were two-tailed and a probability value <0.05 was considered statistically significant.

RESULTS

The mean age of the analytic study sample was 54.3 ± 12.4 years, and 62.7% were women.

Table 1 Age-adjusted Spearman correlations coefficients between serum leptin concentrations and anthropometric variables by sex among participants in the Jackson Heart Study, 2000–2004

Adiposity measure	Serum leptin*	
	Men	Women
Total body weight, kg	0.68	0.62
BMI, kg/m ²	0.72	0.64
Waist circumference, cm	0.76	0.60

*All $P < 0.001$.

Approximately 86% of the participants were either overweight or obese. Mean leptin levels were significantly lower in men than in women (men: 11.3 vs. women: 37.1 ng/ml, P value < 0.001) and were highly correlated with anthropometric measures (Table 1).

In men, the prevalence of current cigarette smoking and mean pack-years of cigarette smoking were inversely associated with leptin (Table 2). Men with the lowest leptin concentration (quartile 1) had lower levels of anthropometric measures than men with the highest leptin concentration (quartile 4). Unadjusted mean FEV₁, FEV₆, and FVC maximum and % predicted values were inversely associated with leptin

Table 2 Sex-specific characteristics across circulating serum leptin quartiles among participants in the Jackson Heart Study, 2000–2004

Characteristics	Serum leptin concentrations, ng/ml				P for trend
	Quartile 1 (0.8–4.8), $N = 429$	Quartile 2 (4.9–8.5), $N = 441$	Quartile 3 (8.6–14.1), $N = 435$	Quartile 4 (14.2–106.9), $N = 437$	
Men					
Age, years	52.8 (12.9)	54.1 (12.0)	54.1 (12.1)	53.5 (13.1)	0.405
Less than high-school diploma, %	19.8	16.6	20.2	14.4	0.065
Current smoker, %	28.4	17.5	14.5	12.4	< 0.001
Former smoker, %	22.6	27.2	23.9	26.3	0.557
Pack-years of smoking	7.2 (10.0)	7.0 (10.5)	5.5 (9.5)	5.2 (9.0)	0.004
Respiratory medication use, %	2.6	2.5	3.2	3.4	0.796
Total body weight, kg	79.4 (14.3)	89.0 (12.6)	95.7 (13.3)	114.8 (22.9)	< 0.001
BMI, kg/m ²	25.3 (4.1)	28.2 (3.3)	30.4 (3.5)	36.0 (6.5)	< 0.001
Waist circumference, cm	88.4 (8.6)	97.3 (8.1)	102.8 (8.6)	117.3 (15.5)	< 0.001
FEV ₁ % predicted	93.1 (18.2)	89.4 (16.4)	89.6 (15.4)	85.0 (16.2)	< 0.001
FEV ₆ % predicted	95.3 (16.9)	89.5 (14.3)	89.2 (13.3)	84.9 (15.4)	< 0.001
FVC% predicted	94.5 (17.1)	88.6 (14.2)	88.0 (13.5)	84.2 (18.3)	< 0.001
	Quartile 1 (1.4–22.3), $N = 727$	Quartile 2 (22.4–33.0), $N = 740$	Quartile 3 (33.1–46.7), $N = 733$	Quartile 4 (46.8–145.6), $N = 737$	P for trend
Women					
Age, years	54.9 (13.0)	55.4 (11.8)	54.3 (12.3)	54.2 (12.2)	0.238
Less than high-school diploma, %	16.8	16.5	15.2	16.2	0.735
Current smoker, %	14.3	10.6	7.7	6.7	< 0.001
Former smoker, %	15.3	13.1	16.5	16.6	0.288
Pack-years of smoking	3.7 (7.6)	2.7 (6.4)	2.9 (6.8)	2.8 (6.9)	0.041
Respiratory medication use, %	4.1	5.6	3.6	7.1	0.014
Menopause status, %	67.6	70.8	68.4	72.0	0.186
Total body weight, kg	72.7 (14.2)	83.4 (15.2)	91.6 (15.7)	106.5 (20.7)	< 0.001
BMI, kg/m ²	26.9 (4.9)	31.0 (5.3)	34.1 (5.6)	39.5 (7.3)	< 0.001
Waist circumference, cm	87.7 (11.5)	97.3 (12.5)	103.1 (13.7)	113.6 (16.4)	< 0.001
FEV ₁ % predicted	95.6 (19.6)	95.1 (16.5)	92.6 (17.4)	89.6 (16.3)	< 0.001
FEV ₆ % predicted	96.5 (18.6)	94.5 (16.8)	92.6 (17.7)	88.7 (15.5)	< 0.001
FVC% predicted	95.6 (19.9)	93.4 (17.6)	92.0 (19.4)	87.7 (16.0)	< 0.001

FEV₁, forced expiratory volume in 1 s; FEV₆, forced expiratory volume in 6 s; FVC, forced vital capacity.

Table 3 Multivariable adjusted least-square mean lung function values across quartiles of serum leptin by sex among participants in the Jackson Heart Study, 2000–2004

Lung function	Model 1			Model 2		
	Total (n = 4,679)	Men (n = 1,742)	Women (n = 2,937)	Total (n = 4,679)	Men (n = 1,742)	Women (n = 2,937)
FEV ₁ % predicted						
Quartile 1	95.0	93.4	95.7	93.6	92.7	94.1
Quartile 2	93.0	89.4	95.1	92.7	89.4	94.7
Quartile 3	91.4	89.9	92.5	91.6	90.0	92.7
Quartile 4	88.0	84.9	90.0	89.5	85.6	91.7
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.021
FEV ₆ % predicted						
Quartile 1	96.3	95.3	96.6	94.5	94.1	94.5
Quartile 2	92.8	89.6	94.6	92.3	89.3	94.1
Quartile 3	91.2	89.4	92.4	91.5	89.5	92.8
Quartile 4	87.4	85.0	88.9	89.3	86.3	91.1
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.009
FVC% predicted						
Quartile 1	95.4	94.4	95.7	93.5	93.0	93.6
Quartile 2	91.6	88.6	93.4	91.2	88.3	92.9
Quartile 3	90.4	88.2	91.8	90.6	88.3	92.2
Quartile 4	86.5	84.4	87.9	88.6	86.0	90.2
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.028

For men, quartile 1 is ≤ 4.8 ; quartile 2 is > 4.8 to ≤ 8.5 ; quartile 3 is > 8.5 to ≤ 14.1 ; and, quartile 4 is > 14.1 ng/ml. For women, quartile 1 is ≤ 22.4 ; quartile 2 is > 22.4 to ≤ 33.2 ; quartile 3 is > 33.2 to ≤ 46.8 ; and, quartile 4 is > 46.8 ng/ml. Model 1 is adjusted for age, education, current smoking status, pack-years of cigarette smoking, current respiratory medication use, and menopause status (in women). Model 2 is further adjusted for total body weight, waist circumference, and BMI. FEV₁, forced expiratory volume in 1 s; FEV₆, forced expiratory volume in 6 s; FVC, forced vital capacity.

concentrations. Similar relationships were observed among women. The prevalence of respiratory medication use generally increased with increasing leptin quartiles among women, although the trend was not always linearly patterned. No clear patterns were observed for menopause status among women.

After adjustment for potential confounders (model 1), leptin was inversely associated with FEV₁, FEV₆, and FVC% predicted in men (all $P < 0.001$) and women (all $P < 0.001$; **Table 3**). These inverse associations were generally graded with mean lung function values decreasing progressively across increasing quartiles of leptin, suggesting a dose–response relationship. Adjustment for total body weight, waist circumference, and BMI did not substantially attenuate the associations between leptin and lung function (model 2). Mean differences in lung function values between men in quartile 1 compared to men in quartile 4 were greater than the mean differences between women in quartile 1 compared to women in quartile 4 before (model 1) and after (model 2) adjustment for adiposity.

There were significant interactions between serum leptin and BMI on FEV₁ (P value < 0.001), FEV₆ (P value = 0.020), and FVC (P value = 0.045) % predicted for men and women in age-adjusted models, suggesting that the associations between leptin and lung function differ by BMI category. Therefore, we further stratified the analyses by BMI category (i.e., normal weight: $18.5 \geq \text{BMI} < 25.0$; overweight: $25.0 \geq \text{BMI} < 30$; obese:

$\text{BMI} \geq 30$). In fully adjusted models, leptin was inversely associated with FEV₁ (upper panel), FEV₆ (middle panel), and FVC (lower panel) % predicted among men in all BMI categories (**Figure 1**). These relationships were most consistently graded among normal-weight men. Among women, statistically significant inverse trends of leptin with lung function were generally observed among obese women, although there was some evidence of a significant inverse trend of leptin with FEV₁ % predicted among overweight women (**Figure 1**, upper panel). No significant trends were observed among normal-weight women.

DISCUSSION

In this population of middle-aged and elderly African-American men and women, we found that higher serum leptin levels was associated with lower FEV₁, FEV₆, and FVC% predicted values. Patterns tended to be graded with mean lung function values progressively decreasing across increasing categories of leptin, suggesting a dose–response relationship. Associations persisted after adjustment for potential confounders, and differences in the mean lung function values between men in the highest and lowest quartile of leptin values were greater compared to that of women. BMI modified the association between leptin and lung function, especially in women: leptin was most consistently associated with lung function in obese women, less consistent

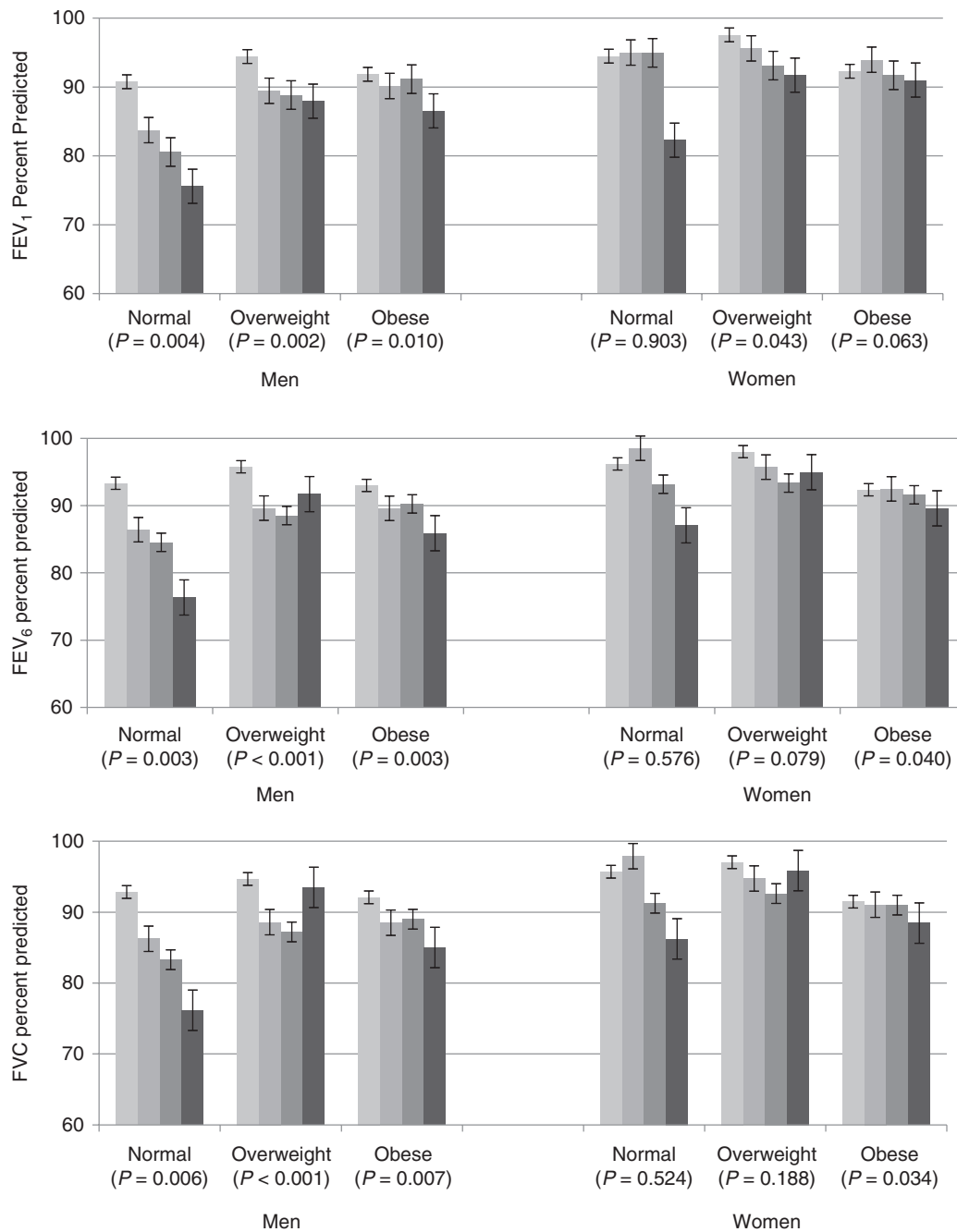


Figure 1 Adjusted mean (a) FEV₁, (b) FEV₆, and (c) FVC% predicted values across leptin quartile, stratified by sex and BMI: Jackson Heart Study, 2000–2004. Mean lung function values (and standard errors) were obtained from multivariable models adjusted for age, education, current cigarette smoking status, pack-years of cigarette smoking, respiratory medication use, menopause status (in women), total body weight, waist circumference, and BMI. *P* for trend was obtained by including leptin as an ordinal variable in fully adjusted models. FEV₁, forced expiratory volume in 1 s; FEV₆, FEV in 6 s; FVC, vital capacity.

in overweight women, and absent in normal-weight women. Overall, our findings support the hypothesis that increased levels of circulating serum leptin may be inversely associated with lung function in African Americans.

Previous studies looking at predominantly white (36) and national (40) populations support our findings. In a predominantly non-Hispanic white cohort of 135 patients with stable systolic heart failure, leptin was independently and inversely

associated with FEV₁ and FVC% predicted. Similar to our cohort, adjusting for percent body fat did not significantly attenuate the association between leptin and lung function. Sierra-Johnson *et al.* (36) also found that serum leptin explained ~5% of the variation in FEV₁ and FVC% predicted values. We found somewhat similar variability between leptin and lung function in men, but not women. The variation ranged from 2.1% (FEV₆% predicted) to 5.4% (FEV₁% predicted) in men

and from 1.4% (FEV₁% predicted) to 2.5% (FEV₆% predicted), suggesting potential differences by sex (data not shown). On average, adiposity explained 4% of the variation, followed by current cigarette smoking and pack-years of smoking (3%), respiratory medication use (2%), menopause status (1%), and sociodemographic characteristics (0.05; data not shown).

Investigators in the NHANES study hypothesized that poor respiratory function contributes to the pathogenesis of cardiovascular outcomes by increasing circulating serum leptin levels (40). Animal studies, however, indicate that circulating leptin concentrations regulate physiological responses of the lungs. Six isoforms of the leptin receptor have been discovered in lung tissue, and the functional Ob-Rb isoform, the longest receptor isoform, has acutely high concentrations in epithelial cells in the lungs (25). A study investigating the function of leptin receptors in mouse and human lungs reported that leptin receptors also exist in human lungs and that increases in serum leptin have stimulatory effects on the human respiratory system (24,25). Further research into the potential role of hyperleptinemia in lung toxicity is warranted.

Withstanding methodological differences, Sin *et al.* (40) observed that normal body weight men and women with reduced lung function, defined as FEV₁% predicted, had higher circulating serum leptin levels after adjustment for age, sex, smoking status, and BMI. Gradients based on these NHANES data, however, were observed among an undifferentiated group of “nonwhites” that comprised roughly 25% of the sample. The limited sample of African Americans and restriction to normal-weight individuals did not provide enough statistical power to assess the leptin gradients within other ethnic populations and non-normal-weight populations. A strength of the JHS results is that they are derived from an all-African-American cohort of middle-aged and elderly African-American men and women, a population not extensively examined in previous research. The JHS data provide a much broader picture of African Americans, especially in the Southeastern United States where states such as Mississippi lead the nation in terms of cardiovascular disease and obesity. Specifically, 86.4% of this population sample was either overweight (32.5%) or obese (53.9%), and these rates are far higher than national averages (48). As also seen in our study, nearly 80% of African Americans in Mississippi are overweight or obese, with an estimated 45% classified as obese (49). Taken together, our findings are critically important to understanding the metabolic derangements in states of obesity and the impact on pulmonary function.

Our findings further expand the investigation of examining the associations of serum leptin with lung function to include the interaction of BMI and leptin on lung function. We observed that leptin gradients in lung function are consistent among normal-weight men, with moderate consistency in overweight and obese men, and less consistency in women. The inverse associations of leptin with lung function among men, regardless of BMI status, suggest that elevated leptin levels (and potentially increased total body fat) are associated with reduced lung function in men. In women, lung function showed stronger associations with leptin among obese women.

This could reflect other factors (aside from respiratory dysregulation associated with leptin) in shaping lung function profiles in normal-weight and overweight women. For example, we observed that current cigarette smoking (and pack-years of cigarette smoking) was associated with lower serum leptin levels in men and women. Although it has been well established that smoking diminishes lung function (50), smoking is also an appetite suppressant (51). Individuals who smoke may have lower leptin levels as a consequence of suppressed appetite and food intake, especially in women. Additional investigations in other large African-American samples are needed to confirm these patterns.

This study is specific for African Americans and may not be generalizable to other ethnic populations and less obese populations. We believe that these results may be generalizable to African-American population in the Southeastern United States. Causal pathways between circulating leptin concentrations and lung function cannot be inferred from cross-sectional analyses such as from this study. Additionally, airway mucosa leptin concentrations were not measured. By not doing so, we were unable to assess airway inflammation. Blood collection was not performed in accordance to menstrual cycle in premenopausal women nor was pregnancy information obtained, as leptin levels are higher in pregnant women (52) and women undergoing estrogen or progesterone therapy (53). Though we did not observe a significant interaction between menopausal status and leptin among women ($P > 0.10$), we controlled for menopausal status in the multivariable regression analyses to minimize any potential residual confounding.

This study has several notable strengths. This is the first population-based study to examine the associations of serum leptin, adiposity, and lung function among a large cohort of middle-aged and elderly African-American men and women with spirometry data. Standardized pulmonary function measurements were used to examine the associations of leptin with three measures of lung function. The large sample size enabled us to stratify the analyses and examine heterogeneity by sex and BMI, major limitations of previous studies, and by menopausal status in women, although no significant differences in lung function measures between pre- and postmenopausal women were observed.

Alarming nationwide rates of obesity, especially abdominal obesity, and the racial disparities in obesity-related outcomes suggest the need for the development of new therapeutic target sites to prevent the loss of lung function. In 2003–2004, the overall obesity rate was 32.2% (45) and an excess of 280,000 deaths were attributable to obesity (54). African Americans experience higher death rates from obesity-related causes and respiratory complications compared to whites. Our results suggest that serum leptin concentrations are strongly and inversely associated with lung function in this population, even after adjustment for measures of obesity. There is a growing body of evidence demonstrating the increased cardiovascular risk among persons with impaired lung function (1–4). Further examination of a potential role for serum leptin in these two high-risk disorders has been suggested (40) and prospective studies are warranted.

ACKNOWLEDGMENTS

We give sincere thanks to the Jackson Heart Study participants, staff, and interns for their long-term commitment to the study. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institutes of Health or the National Institute for Occupational Safety and Health. This work was supported by National Institutes of Health: National Heart Lung & Blood Institute and National Center on Minority Health and Health Disparities (contracts N01-HC-95170, N01-HC-95171, and N01-HC-95172).

DISCLOSURE

The authors declared no conflict of interest.

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