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RESPIRATORY MECHANICS

Diabetes, Impaired Glucose Tolerance, and Metabolic Biomarkers in Individuals with Normal Glucose Tolerance are Inversely Associated with Lung Function: The Jackson Heart Study

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Abstract The objectives of this study were to test the hypothesis that diabetes and impaired glucose tolerance (IGT), diabetes control and diabetes duration, and metabolic biomarkers in adults with normal glucose tolerance (NGT) are inversely associated with spirometry-measured lung function. We conducted a cross-sectional observational cohort study that included nonsmoking African American adults ($n = 2{,}945$; mean age = 52.5 ± 12.6 years; 69.2% female), who were free of cardiovascular disease, from the Jackson Heart Study. The interventions were diabetes, metabolic biomarkers and lung function. We measured the associations of glycemia with forced expiratory volume (FEV) in 1 s, FEV in 6 s, and vital capacity. Multivariable adjusted mean lung function values were lower among adults with diabetes and IGT (in women only, but not after adjustment for waist circumference) than adults with NGT. Among adults with diabetes, no associations were observed between lung function and diabetes control or duration. In women with NGT, lower lung function was consistently associated with higher glucose levels and less consistently with higher insulin levels and insulin resistance. Lower lung function was consistently associated with higher insulin levels and insulin resistance and less consistently associated with insulin and hemoglobin A1c in men with NGT. Overall, our findings generally support the hypothesis that diabetes, IGT, and increased levels of metabolic biomarkers in individuals with NGT are inversely associated with lung function in African Americans, independent of adiposity.

Keywords Forced expiratory volume in 1 s · Insulin resistance · Spirometry · Vital capacity · Impaired glucose tolerance

Introduction

Reduced lung function is a significant predictor of cardiovascular and all-cause mortality [1, 2]. The metabolic factors involved in the pathogenesis of disease mortality, however, are understudied in non-White populations. This is of particular public health importance given that African Americans have different lung capacity and dynamics [3] and greater diabetes morbidity and related mortality [4]

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than whites. Epidemiologic studies have demonstrated that individuals with diabetes have a lower forced expiratory volume in 1 s (FEV_1) and lower vital capacity (FVC) than individuals without diabetes [5–10], but these associations have been confounded by smoking and other potential confounders. Reductions of 94 ml of FEV_1 and of 166 ml of FVC, equivalent to approximately 3 and 7 years of age-related lung function loss, have been observed in the early onset of diabetes [11]. Higher glycosylated hemoglobin A1c (HbA1c) levels in adults with diabetes [12] and higher levels of metabolic biomarkers in individuals without diabetes [6, 7, 13, 14] have also been shown to be associated with lower lung function. These findings, however, have been inconsistent [5–16]. In a sample of predominantly white women and men from the Rancho Bernardo Study, Barrett-Conner and Frette [16] observed no association between known or newly diagnosed diabetes and lung function. Moreover, no association was observed between fasting glucose and lung function in women without diabetes. Therefore, gaining a better understanding of the mechanisms through which diabetes and metabolic biomarkers may affect lung function in African Americans could yield important insights into racial disparities in respiratory morbidity and mortality.

The purpose of this study was to investigate the associations of diabetes (prevalence, control, and duration), impaired glucose tolerance (IGT), and metabolic biomarkers in individuals with normal glucose tolerance (NGT) with spirometry-measured lung function among a population-based cohort of nonsmoking African American adults residing in the Southeastern US who were free of cardiovascular disease (CVD). Using data from the Jackson Heart Study (JHS), we hypothesized that adults with diabetes and IGT would have lower lung function than adults with NGT; that uncontrolled diabetes and duration of diabetes would be inversely associated with lung function; that higher levels of glucose, insulin, insulin resistance, and HbA1c among adults with NGT would be inversely associated with lung function; and that these associations would be independent of adiposity.

Methods

The JHS is an observational cohort study of cardiovascular, renal, and respiratory diseases in African American adults residing in a three-county metropolitan area in central Mississippi [17]. Noninstitutionalized African Americans between the ages of 35 and 84 were recruited from households in 102 US Census tracts [18]; eligible family members ≥21 years old were recruited for participation in the JHS Family Study [19]. Nearly one-third of the cohort comprised Atherosclerosis Risk in Communities study participants from the Jackson, MS, site. Other cohort members consisted of volunteer (30%) and randomly selected (17%) residents. A total of 5,301 participants (mean age ± SD = 55 ± 13 years; range = 21–94 years; 63% female) underwent clinical exams, including spirometry, provided blood samples, and completed medical and smoking history questionnaires. Participants provided written consent and the JHS study protocol was approved by the Institutional Review Boards of Jackson State University, Tougaloo College, and the University of Mississippi Medical Center.

Participants with a history of smoking ($n = 1{,}689$) were excluded from this analysis; it has been well established that smoking diminishes lung function and is a major risk factor for chronic obstructive pulmonary disease [20]. Furthermore, examining these associations among never smokers reduces the possibility that the observed associations may be attributed to residual confounding due to smoking. Participants with a self-reported history of a physician-diagnosed myocardial infarction, stroke, or coronary revascularization or evidence of a myocardial infarction by electrocardiogram ($n = 271$) were also excluded as these events often reduce lung function. Of the remaining 3,341 participants, 3,172 performed spirometry that met American Thoracic Society (ATS) criteria for equipment performance, acceptability of each maneuver, and test repeatability [21]. Participants missing the diabetes classification criteria information ($n = 80$), metabolic biomarkers ($n = 84$), or covariates information ($n = 30$) were also excluded. Participants who were older than 80 years ($n = 33$) were excluded because the spirometric reference equations developed from the third examination of the National Health and Nutrition Examination Study [3] were based on healthy African Americans aged 18 years for women and 20 years for men to 80 years, leaving 2,945 participants (mean age = 52.5 ± 12.6 years; range = 21–80 years; 69.2% female) for analysis. The participants included in this analytic sample were slightly older, reported less diabetes, and had a greater proportion of women compared to those participants not included in this study.

Spirometry

Computerized spirometry was used to assess lung function using a dry rolling sealed spirometer (Occupational Marketing, Houston, TX) and was performed in accordance to the ATS 1994 recommendations [21]. Spirometry was performed between the hours of 0700 and 1400 in the JHS Pulmonary Function Lab. The spirometer was calibrated and tested daily for leaks using a 3-L calibrating syringe [22]. Participants were instructed by pulmonary function technicians trained in the proper procedure of using nose clips. Participants performed up to eight maneuvers or until three acceptable with two repeatable maneuvers were achieved. The maximum FEV_1, FEV in 6 s (FEV_6), and FVC values from the three maneuvers with acceptable curves were used in this analysis. Corresponding percent predicted values were calculated using appropriate reference equations [3].

Diabetes and Metabolic Biomarkers

Early morning blood specimens were collected by certified laboratory technicians after an overnight fast of at least 8 h. Glucose and insulin concentrations were measured using standard procedures that met the College of American Pathologists accreditation requirements [22]. A high-performance liquid chromatography system (Tosoh Corporation, Tokyo, Japan) was used to measure glycosylated hemoglobin A1c (HbA1c) concentrations. Diabetes was defined according to the American Diabetes Association (ADA) 2004 criteria [23] as a fasting serum glucose ≥126 mg/dl (≥7.0 mmol/l), self-reported or confirmed use of insulin or oral hypoglycemic medications within 2 weeks of the clinic examination, or a self-report of physician-diagnosed diabetes. Uncontrolled diabetes was defined as an HbA1c level ≥7.0%, in accord with ADA recommendations. Duration of diabetes was defined as the difference in the participant's age at the baseline exam and the self-reported age at which the participant was first told by a doctor that he/she had diabetes. IGT was defined as a fasting glucose >100 mg/dl (>5.5 mmol/l), but ≤125 mg/dl (≤6.7 mmol/l) [23]. Insulin resistance (IR) was determined using the homeostasis model assessment for IR formula [24] and calculated as [fasting insulin (μU/l) × fasting glucose (mmol/l)] ÷ 22.5.

Covariates

Risk factors for reduced lung function [25–27] included education, income, physical activity, respiratory medication use, body mass index (BMI), and waist circumference. Participants self-reported the highest level of education attained (categorized as <high school diploma and ≥high school diploma) and annual household income from all sources (categorized as <$25,000 and ≥$25,000). Physical activity was defined as a summary score (range = 0–4) of the intensity, frequency, and duration of activities associated with transportation to and from work, school, or running errands and engaging in moderate to vigorous exercise [28]. Respiratory medication use was defined as having used at least one class of respiratory medications within 2 weeks of the baseline clinic visit and details have been reported elsewhere [29]. In-clinic standing height and weight were measured according to standard protocols; BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Waist circumference was measured at the umbilicus using an anthropometric tape and rounded to the nearest centimeter.

Statistical Analysis

An analysis of variance followed by a Tukey multiple-comparison test for continuous variables and a χ^2 test for categorical variables were used to compare differences in the baseline characteristics across the diabetes and GT categories. Linear regression models were used to compute multivariable adjusted mean FEV_1, FEV_6, and FVC % predicted values and compare differences across the diabetes and GT categories. Models were fit in sequence: Model 1 adjusted for education, income, physical activity, and respiratory medication use; Models 2 and 3 further adjusted for BMI and waist circumference in separate models; and Model 4 adjusted for BMI and waist circumference in combination. The associations between metabolic biomarkers and lung function in participants with NGT were examined using the same modeling sequence. The statistical significance of any trends in the patterning of lung function across levels of metabolic biomarkers was determined by including the metabolic biomarkers as an ordinal covariate (i.e., divided into quartiles) in the models. The variance inflation factor for BMI and waist circumference exceeded three when both covariates were simultaneously added to the model for each lung function measure, suggesting collinearity. We present data for waist circumference adjustment (Model 3) heretofore as waist circumference has been shown in previous work [27] to be a stronger predictor of reduced lung function than BMI. Interactions between the diabetes and GT categories and metabolic biomarkers and sex, BMI, and waist circumference on the lung function measures were tested in multivariable adjusted models (Model 1). There were significant interactions between diabetes and GT and sex ($p_s < 0.05$) and between the metabolic biomarkers and sex ($p_s < 0.05$) on FEV_1, FEV_6, and FVC % predicted, suggesting different effects of GT and metabolic biomarkers on lung function in women and men. Therefore, we stratified all analyses by sex. No statistically significant interactions of BMI and waist circumference on these associations were observed. All tests were two-tailed and $P < 0.05$ was considered statistically significant. SAS ver. 9.2 (SAS Institute, Cary, NC) was used to conduct all statistical analyses.

Results

The prevalence of diabetes and IGT was 16.3% (women: 17.5%; men: 13.7%) and 12.4% (women: 11.6%; men:

14.2%), respectively. Participants with diabetes and IGT were older, reported lower socioeconomic status, and were more obese and less physically active than participants with NGT (Table 1). Participants with diabetes and IGT (in women only) had significantly lower unadjusted mean FEV$_1$, FEV$_6$, and FVC % predicted values compared to participants with NGT.

In models adjusted for education, annual household income, physical activity, and respiratory medication use (Model 1), mean FEV$_1$, FEV$_6$, or FVC % predicted values were significantly lower among women with diabetes and IGT than among women with NGT (Table 2). The significant mean difference between women with IGT and women with NGT was attenuated ($p_s < 0.10$) after adjustment for waist circumference (Model 2). Similar relationships were observed among men; however, differences in mean lung function values between men with IGT and men with NGT did not reach statistical significance ($P > 0.05$). No significant associations between diabetes control and duration of diabetes and FEV$_1$, FEV$_6$, or FVC % predicted were observed in women or men (data not shown).

All metabolic biomarkers were inversely associated with FEV$_1$ % predicted among women with NGT in models adjusted for education, annual household income, physical activity, and respiratory medication use (Table 3). These trends tended to be graded, suggesting dose–response relationships. Only the inverse associations between glucose and FEV$_1$ % predicted persisted after waist circumference was accounted for in the fully adjusted model (Model 2); the association between HbA1c and FEV$_1$ % predicted was marginal ($P < 0.10$). Graded trends were also observed among men with NGT, although the associations between the metabolic biomarkers and lung function differed. In fully adjusted models, only insulin and IR were inversely associated with FEV$_1$ % predicted in men, even after adjustment for waist circumference (Table 3). In women, higher glucose levels were consistently inversely associated with lower FEV$_6$ and FVC % predicted (Tables 4, 5, respectively). Insulin, IR, and HbA1c were less consistently inversely associated with FEV$_6$ and FVC % predicted in fully adjusted models (Tables 4, 5, respectively). In men, higher insulin and IR levels were consistently associated with lower FEV$_6$ and FVC %

Table 1 Sex-stratified demographic, metabolic biomarkers, and lung function measures by diabetes and glucose tolerance categories among participants in the Jackson heart study, 2000–2004

	Women			Men		
	Diabetes ($n = 357$)	Impaired glucose tolerance ($n = 236$)	Normal glucose tolerance ($n = 1.445$)	Diabetes ($n = 124$)	Impaired glucose tolerance ($n = 129$)	Normal glucose tolerance ($n = 654$)
Age (years)	58.9 ± 10.1***	59.2 ± 10.6***	51.0 ± 12.7	57.6 ± 11.5***	55.1 ± 12.0***	48.6 ± 12.3
<High school diploma (%)	23.3***	19.9***	9.2	19.4***	16.3**	8.3
Household income <$25,000 (%)	37.8***	39.0***	28.0	26.6***	20.2	14.1
Standing height (cm)	163.7 ± 6.2	163.9 ± 6.4	164.0 ± 6.4	177.6 ± 6.8	178.0 ± 6.7	177.5 ± 7.2
Body mass index (kg/m^2)	35.7 ± 7.6***	34.8 ± 6.9***	32.0 ± 7.4	32.1 ± 5.2***	31.9 ± 5.8***	29.8 ± 6.4
Waist circumference (cm)	109.4 ± 17.0***	105.9 ± 15.9***	96.8 ± 16.0	107.8 ± 12.7***	106.3 ± 13.3***	99.6 ± 15.9
Physical activity	2.0 ± 0.8***	2.0 ± 0.8***	2.1 ± 0.8	2.0 ± 0.8*	2.1 ± 0.8	2.2 ± 0.8
Respiratory medication use (%)	5.0	6.4	4.5	1.6	3.9	2.5
Fasting glucose (mg/dl)	–	5.9 ± 0.3***	4.8 ± 0.4	–	5.9 ± 0.3***	4.9 ± 0.3
Fasting insulin (μU/l)	–	140.3 ± 78.8***	93.3 ± 49.3	–	116.6 ± 54.4***	85.9 ± 43.8
Insulin resistance	–	6.2 ± 3.6***	3.3 ± 1.9	–	5.1 ± 2.4***	3.1 ± 1.7
Hemoglobin A1c (%)	7.8 ± 1.8***	6.0 ± 0.6***	5.5 ± 0.4	8.1 ± 2.0***	5.9 ± 0.7***	5.4 ± 0.5
Uncontrolled diabetes (%)	59.7	–	–	64.4	–	–
Duration of diabetes (years)	10.5 ± 9.5	–	–	9.9 ± 8.3	–	–
FEV$_1$ % predicted	90.4 ± 18.4***	92.2 ± 18.9*	95.5 ± 16.9	83.7 ± 16.0***	90.1 ± 18.0	93.2 ± 15.5
FEV$_6$ % predicted	89.6 ± 19.7***	90.9 ± 17.2***	95.0 ± 16.2	82.8 ± 13.0***	89.7 ± 15.8*	92.6 ± 14.9
FVC % predicted	88.4 ± 20.6***	89.7 ± 17.1***	94.0 ± 16.4	81.2 ± 13.2***	89.0 ± 17.5	91.7 ± 15.4

Data are mean ± SD or percentage

FEV$_1$ forced expiratory volume in 1 s; *FEV$_6$* forced expiratory volume in 6 s; *FVC* orced vital capacity

Participants with a normal glucose tolerance served as the referent group. χ^2 tests were used for categorical variables and analysis of variance followed by a Tukey multiple comparison test for continuous variables

† $P < 0.10$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 2 Sex-stratified adjusted mean lung function values by diabetes and glucose tolerance categories among participants in the Jackson heart study, 2000–2004

Lung function variable	Women			Men		
	Diabetes ($n = 357$)	Impaired glucose tolerance ($n = 236$)	Normal glucose tolerance ($n = 1.445$)	Diabetes ($n = 124$)	Impaired glucose tolerance ($n = 129$)	Normal glucose tolerance ($n = 654$)
FEV_1 % predicted						
Model 1	90.5***	92.4***	95.5	84.2***	90.7	93.0
	(88.7–92.3)	(90.2–94.6)	(94.6–96.4)	(81.4–86.9)	(88.0–93.4)	(91.8–94.2)
Model 2	92.2*	93.4†	94.9	85.0***	91.4	92.7
	(90.4–94.0)	(91.3–95.6)	(94.0–95.7)	(82.3–87.7)	(88.7–94.0)	(91.5–93.9)
FEV_6 % predicted						
Model 1	89.6***	91.1***	95.0	83.2***	90.1	92.4
	(87.8–91.3)	(88.9–93.2)	(94.1–95.9)	(80.6–85.8)	(87.6–92.6)	(91.3–93.6)
Model 2	91.6**	92.2†	94.3	84.2***	90.9	92.1
	(89.8–93.3)	(90.1–94.4)	(93.5–95.2)	(81.7–86.8)	(88.4–93.4)	(91.0–93.2)
FVC % predicted						
Model 1	88.5***	89.9***	94.0	81.7***	89.4	91.5
	(86.7–90.3)	(87.7–92.1)	(93.1–94.9)	(79.0–84.4)	(86.8–92.0)	(90.4–92.7)
Model 2	90.5***	91.1†	93.3	82.7***	90.2	91.2
	(88.7–92.3)	(88.9–93.2)	(92.4–94.2)	(80.0–85.3)	(87.6–92.8)	(90.0–92.3)

FEV_1 forced expiratory volume in 1 s; *FEV_6* forced expiratory volume in 6 s; *FVC* forced vital capacity

Model 1 adjusts for education, annual household income, physical activity, and respiratory medication use. Model 2 adjusts for the variables in Model 1 plus waist circumference. Participants with a normal glucose tolerance served as the referent group

† $P < 0.10$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

predicted values (Tables 4, 5, respectively). No associations were observed between glucose and lung function in men with NGT.

Discussion

In the current study, diabetes, IGT, and levels of metabolic biomarkers in adults with NGT were inversely and independently associated with lung function in community-dwelling, nonsmoking African American adults who were free of clinical CVD. These associations varied by sex. Women with diabetes and IGT had significantly lower FEV_1, FEV_6, and FVC % predicted values compared to women with NGT, with differences averaging approximately 4–6 and 3–5%, respectively. The mean differences in lung function between women with IGT and NGT did not persist after adjustment for waist circumference. Men with diabetes had significantly lower lung function than men with NGT. No significant associations between uncontrolled diabetes and duration of diabetes and lung function were observed in women or men. Lower lung function was consistently associated with higher glucose and less consistently with higher insulin, IR, and HbA1c levels in women with NGT. In men with NGT, lower lung function was consistently associated with higher insulin and IR levels; no associations were observed between lung function and glucose and HbA1c in men. These associations persisted after adjustment for waist circumference and other potential confounders.

Our findings are consistent with previous studies that explored the associations of diabetes and lung function in cohorts of elderly [13, 16], predominantly white [5, 12, 14–16], and US [6, 10, 11] samples. Our findings extend the literature by investigating the associations between glycemia and lung function in middle-aged and elderly African Americans and estimating lung function in individuals with IGT (i.e., prediabetes). Although the associations between IGT and lung function in African Americans were attenuated after adjustment for waist circumference, the findings observed among African American women with IGT supports the hypothesis of declines in lung function early in the development of diabetes. The lack of association in men may be explained by other physiological processes. Glucose metabolism occurs in the adipose (and muscle) tissue of the abdomen and higher insulin concentrations are needed in the presence of increased adipose tissue volumes in order to enable the body to properly absorb glucose. Men in this cohort have been shown to have higher visceral adipose tissue (VAT)

Table 3 Sex-stratified adjusted mean forced expiratory volume in 1 s% predicted values across quartiles of metabolic biomarkers among participants with normal glucose tolerance in the Jackson heart study, 2000–2004

	Women ($n = 1.445$)					Men ($n = 654$)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend
Glucose (mg/dl)	(68–82)	(83–86)	(87–91)	(92–99)		(71–84)	(85–88)	(89–92)	(93–99)	
Model 1	95.1	96.3	97.0	93.7	0.039	94.9	93.8	91.7	92.3	0.217
	(93.4–96.8)	(94.5–98.2)	(95.3–98.6)	(92.1–95.4)		(92.6–97.2)	(91.5–96.1)	(89.3–94.1)	(90.1–94.5)	
Model 2	94.2	96.3	97.2*	94.4	0.037	94.3	93.8	91.8	92.8	0.459
	(92.5–95.9)	(94.4–98.1)	(95.6–98.8)	(92.8–96.1)		(92.0–96.7)	(91.5–96.0)	(89.4–94.2)	(90.6–95.0)	
Insulin (μU/l)	(1–9)	(10–13)	(14–18)	(19–105)		(1–9)	(10–12)	(13–17)	(18–50)	
Model 1	97.5	96.3	95.5	93.0***	0.005	95.4	94.3	94.4	88.4***	<0.001
	(95.6–99.5)	(94.7–97.9)	(93.8–97.1)	(91.3–94.8)		(93.1–97.6)	(92.1–96.6)	(92.2–96.7)	(86.1–90.7)	
Model 2	95.8	95.9	95.7	94.7	0.802	94.8	94.0	94.6	89.1**	0.005
	(93.8–97.8)	(94.3–97.4)	(94.0–97.3)	(92.9–96.5)		(92.4–97.1)	(91.7–96.3)	(92.3–96.9)	(86.6–91.6)	
Insulin resistance	(0.189–2.161)	(2.162–2.922)	(2.923–4.027)	(4.028–25.009)		(0.179–2.014)	(2.015–2.681)	(2.682–3.840)	(3.841–10.949)	
Model 1	97.5	95.8	95.4	93.3***	0.009	95.4	94.5	94.1	88.7***	<0.001
	(95.9–99.2)	(94.0–97.5)	(93.7–97.1)	(91.6–95.0)		(93.1–97.6)	(92.3–96.8)	(91.9–96.4)	(86.4–91.0)	
Model 2	96.0	95.3	95.8	94.9	0.812	94.8	94.2	94.3	89.4**	0.011
	(94.3–97.8)	(93.6–97.0)	(94.1–97.5)	(93.1–96.7)		(92.4–97.2)	(91.9–96.5)	(92.0–96.5)	(86.9–91.9)	
HbA1c (%)	(3.6–5.1)	(5.2–5.4)	(5.5–5.7)	(5.8–7.6)		(3.6–5.1)	(5.2–5.4)	(5.5–5.7)	(5.8–7.9)	
Model 1	96.9	97.1	94.4*	93.8*	0.016	93.8	94.8	94.1	90.3*	0.038
	(95.1–98.6)	(95.3–98.9)	(92.8–96.0)	(92.1–95.6)		(91.5–96.2)	(92.4–97.2)	(91.9–96.2)	(87.9–92.6)	
Model 2	96.0	96.7	94.6	94.8	0.281	93.4	94.6	94.2	90.8	0.109
	(94.3–97.8)	(95.0–98.5)	(93.0–96.3)	(93.0–96.6)		(91.0–95.7)	(92.2–96.9)	(92.0–96.3)	(88.4–93.1)	

HbA1c hemoglobin A1c

Model 1 adjusts for education, annual household income, physical activity, and respiratory medication use. Model 2 adjusts for the variables in Model 1 plus waist circumference. Participants in quartile 1 served as the referent group

† $P < 0.10$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 4 Sex-stratified adjusted mean forced expiratory volume in 6 s% predicted values across quartiles of metabolic biomarkers among participants with normal glucose tolerance in the Jackson heart study, 2000–2004

	Women (n = 1.445)					Men (n = 654)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p for trend	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p for trend
Glucose (mg/dl)	(68–82)	(83–86)	(87–91)	(92–99)		(71–84)	(85–88)	(89–92)	(93–99)	
Model 1	94.2	95.3	97.0*	93.6	0.017	93.9	93.1	91.8	91.6	0.447
	(92.6–95.8)	(93.5–97.1)	(95.4–98.6)	(92.0–95.2)		(91.6–96.2)	(90.8–95.3)	(89.5–94.2)	(89.5–93.8)	
Model 2	93.2	95.2	97.3***	94.4	0.004	93.2	93.0	92.0	92.3	0.870
	(91.5–94.8)	(93.5–96.9)	(95.7–98.8)	(92.8–96.0)		(90.9–95.4)	(90.8–95.2)	(89.6–94.3)	(90.1–94.4)	
Insulin (μU/l)	(1–9)	(10–13)	(14–18)	(19–105)		(1–9)	(10–12)	(13–17)	(18–50)	
Model 1	97.3	96.4	94.9	91.8***	<0.001	95.9	93.7	93.6	86.9***	<0.001
	(95.4–99.1)	(94.9–98.0)	(93.4–96.5)	(90.1–93.4)		(93.7–98.0)	(91.5–95.9)	(91.3–95.8)	(84.6–89.2)	
Model 2	95.3	95.9	95.2	93.7	0.328	95.1	93.3	93.8	87.9***	<0.001
	(93.3–97.2)	(94.4–97.4)	(93.6–96.7)	(92.0–95.4)		(92.8–97.3)	(91.1–95.5)	(91.6–96.0)	(85.5–90.4)	
Insulin resistance	(0.189–2.161)	(2.162–2.922)	(2.923–4.027)	(4.028–25.009)		(0.179–2.014)	(2.015–2.681)	(2.682–3.840)	(3.841–10.949)	
Model 1	97.1	96.0	94.7*	92.2***	<0.001	95.6	94.3	93.2*	87.2***	<0.001
	(95.5–98.8)	(94.4–97.7)	(93.0–96.3)	(90.6–93.9)		(93.4–97.8)	(92.1–96.5)	(91.0–95.4)	(85.0–89.4)	
Model 2	95.4	95.5	95.1	94.1	0.686	94.8	93.9	93.4	88.2***	0.001
	(93.7–97.1)	(93.8–97.1)	(93.5–96.8)	(92.4–95.8)		(92.5–97.1)	(91.7–96.1)	(91.2–95.6)	(85.8–90.7)	
HbA1c (%)	(3.6–5.1)	(5.2–5.4)	(5.5–5.7)	(5.8–7.6)		(3.6–5.1)	(5.2–5.4)	(5.5–5.7)	(5.8–7.9)	
Model 1	97.3	96.4	93.6**	92.8***	<0.001	93.5	94.3	93.3	89.4*	0.016
	(95.6–98.9)	(94.7–98.0)	(92.0–95.1)	(91.1–94.5)		(91.2–95.8)	(92.0–96.7)	(91.2–95.4)	(87.1–91.7)	
Model 2	96.3	95.9	93.9*	93.9†	0.077	93.0	94.0	93.4	90.0	0.085
	(94.6–97.9)	(94.3–97.6)	92.3–95.4)	(92.2–95.6)		(90.7–95.2)	(91.7–96.3)	(91.3–95.5)	(87.7–92.3)	

HbA1c hemoglobin A1c

Model 1 adjusts for education, annual household income, physical activity, and respiratory medication use. Model 2 adjusts for the variables in Model 1 plus waist circumference. Participants in quartile 1 served as the referent group

† $P < 0.10$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 5 Sex-stratified adjusted mean forced vital capacity % predicted values across quartiles of metabolic biomarkers among participants with normal glucose tolerance in the Jackson heart study, 2000–2004

	Women (n = 1.445)					Men (n = 654)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend
Glucose (mg/dl)	(68–82)	(83–86)	(87–91)	(92–99)		(71–84)	(85–88)	(89–92)	(93–99)	
Model 1	93.2	94.2	96.0*	92.7	0.026	93.1	92.4	90.8	90.5	0.364
	(91.5–94.8)	(92.4–96.0)	(94.4–97.6)	(91.0–94.3)		(90.7–95.4)	(90.0–94.7)	(88.4–93.2)	(88.3–92.8)	
Model 2	92.1	94.1	96.2***	93.5	0.005	92.3	92.3	90.9	91.2	0.784
	(90.5–93.8)	(92.3–95.9)	(94.6–97.8)	(91.9–95.1)		(90.0–94.7)	(90.0–94.6)	(88.5–93.3)	(89.0–93.4)	
Insulin (μU/l)	(1–9)	(10–13)	(14–18)	(19–105)		(1–9)	(10–12)	(13–17)	(18–50)	
Model 1	96.3	95.5	93.9	90.6***	<0.001	94.9	92.8	92.7	86.0***	<0.001
	(94.4–98.2)	(94.0–97.1)	(92.3–95.5)	(88.9–92.3)		(92.7–97.1)	(90.5–95.1)	(90.4–95.0)	(83.6–88.3)	
Model 2	94.3	95.0	94.1	92.6	0.244	94.1	92.4	92.9	87.0***	<0.001
	(92.3–96.2)	(93.5–96.6)	(92.5–95.7)	(90.8–94.3)		(91.7–96.4)	(90.1–94.7)	(90.6–95.2)	(84.5–89.5)	
Insulin resistance	(0.189–2.161)	(2.162–2.922)	(2.923–4.027)	(4.028–25.009)		(0.179–2.014)	(2.015–2.681)	(2.682–3.840)	(3.841–10.949)	
Model 1	96.1	95.2	93.6*	91.1***	<0.001	94.4	93.7	92.2*	86.2***	<0.001
	(94.4–97.8)	(93.6–96.9)	(91.9–95.2)	(89.4–92.8)		(92.2–96.7)	(91.5–96.0)	(89.9–94.5)	(83.9–88.5)	
Model 2	94.3	94.7	94.0	93.0	0.594	93.6	93.3	92.4	87.3***	0.002
	(92.6–96.1)	(93.0–96.3)	(92.4–95.7)	(91.3–94.7)		(91.3–96.0)	(91.0–95.6)	(90.1–94.7)	(84.8–89.8)	
HbA1c (%)	(3.6–5.1)	(5.2–5.4)	(5.5–5.7)	(5.8–7.6)		(3.6–5.1)	(5.2–5.4)	(5.5–5.7)	(5.8–7.9)	
Model 1	96.4	95.2	92.4***	91.7***	<0.001	92.6	93.7	92.3	88.3*	0.012
	(94.7–98.1)	(93.5–96.9)	(90.8–94.0)	(89.9–93.4)		(90.2–95.0)	(91.3–96.1)	(90.1–94.4)	(85.9–90.7)	
Model 2	95.4	94.8	92.7*	92.8*	0.048	92.1	93.4	92.4	$89.0^{\dagger}$	0.064
	(93.8–97.1)	(93.1–96.5)	(91.2–94.3)	(91.1–94.5)		(89.7–94.4)	(91.0–95.8)	(90.3–94.5)	(86.6–91.3)	

HbA1c hemoglobin A1c

Model 1 adjusts for education, annual household income, physical activity, and respiratory medication use. Model 2 adjusts for the variables in Model 1 plus waist circumference. Participants in quartile 1 served as the referent group

† $P < 0.10$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

volumes than women [30]. This may contribute to the production of higher concentrations of insulin in the body, resulting in reduced lung function in men. Moreover, the lack of associations between diabetes control and duration of diabetes in women and men in this cohort may be due to the small number of participants with severe uncontrolled diabetes (mean = 7.9 ± 1.8%), or the small number of participants with a prolonged duration of diabetes (mean = 10.3 ± 9.3 years). A study among older adults, however, reported that duration of diabetes (>10 years) was associated with lower FEV_1 and FVC in white men only [16].

Prior work that examined the associations of metabolic biomarkers with lung function is more obscure. First, studies examining these associations have been confounded by smokers and individuals with IGT and the findings have been mixed [6, 7, 9, 12–16]. Second, few studies have investigated differences by sex. In the present study, we observed significant heterogeneity in the association between metabolic biomarkers and lung function by sex. In addition, in our sample of nonsmoking adults with NGT, we observed that lower lung function was consistently associated with higher glucose levels in women and higher insulin levels and IR in men. In the predominantly white Rancho Bernardo Study, plasma glucose levels were inversely associated with FEV_1 and FVC in men without diabetes, but not in women. Investigators from the British Women's Heart and Health Study [7] reported that IR was inversely associated with these lung function measures among nonsmoking British women who were 60–79 years of age after adjusting for height, BMI, waist-to-hip ratio, physical activity, white blood cell count, socioeconomic status, and respiratory medication use. Burchfiel et al. [13] reported that fasting insulin was inversely associated with FVC in elderly Japanese American men with a history of smoking. These studies, however, did not exclude individuals with IGT, which may contribute to differences in these findings (notwithstanding obvious racial/ethnic and geographic differences).

Diabetes is a metabolic disease marked by high levels of glucose in the blood and is linked to conditions such as retinopathy, neuropathy, and nephropathy [31]. Lung injury occurs via microangiopathy—structural and functional alterations of capillaries in the alveolar septa and arterioles—in states of diabetes [32]. Lung biopsies from patients with diabetes have shown thickening of the alveolar epithelial and endothelial capillary basal lamina [32]. An animal study observed narrowing of the lumen of alveolar capillary endothelial cells and an uneven distribution of the anionic sites of endothelial capillaries exposed by the luminal plasmalemma [33]. In human lungs, structural and functional changes in the state of diabetes also include the alteration of the biochemistry of connective tissue in the human lungs [34]. The most consistent abnormalities are reduced volumes and elastic recoil, which results from increased lysyl oxidase activity and glycosylation-induced compositional changes of collagen [34, 35].

The mechanisms that explain the relationships of metabolic biomarkers with lung function in women and men may reflect different physiologic pathways. The inverse association of insulin with lung function (except for FVC) in women did not remain significant after adjustment for waist circumference, suggesting that other metabolic dysregulations in states of obesity, possibly systemic and vascular inflammation, contribute to reduced lung function in women. The association of HbA1c with lung function in women and men may be expected since HbA1c is a glucose-protein derivative and reflects an integrated measure of glucose control in the body over time. Men have been shown to have greater VAT volumes than women [30], and greater intra-abdominal fat in the abdomen has been shown to play an important role in the development of IR [36] and reduced lung function [37]. Additional investigations with longitudinal study designs and multiethnic populations are needed to fully understand lung function in states of NGT.

Causal pathways of GT, diabetes control and duration of diabetes, and metabolic biomarkers in individuals with NGT and lung function cannot be inferred from cross-sectional analyses such as the current study. The general consistency and strength of these relationships in different racial/ethnic populations, however, indicate that GT and metabolic biomarkers play an important role in reduced lung function. However, emerging evidence hypothesizes that reduced lung function is a predictor of incident diabetes [10, 38], suggesting a potential bidirectional relationship. The fact that our sample consisted of generally healthy adults who never smoked supports the hypothesis that the lungs are a target organ in diabetes and glycemia. The exposure to environmental tobacco smoke and other environmental toxicants cannot be dismissed. Studies have observed that environmental tobacco smoke and chronic exposure to traffic-related pollution is associated with reduced lung function [39, 40]. Environmental pollution levels are considerably lower in this region of the US compared to other metropolitan areas and the geographic regions in which participants were sampled are predominantly mixed urban–rural and rural areas [41]. Thus, we are not led to believe that such exposures would mediate the findings reported in this study.

Overall, our findings support the hypothesis that diabetes, IGT, and higher levels of metabolic biomarkers in individuals with NGT are associated with reduced lung function in African Americans, generally after adjustment for abdominal adiposity. There is a growing literature that demonstrates an increased cardiovascular risk among persons with reduced lung function [1, 2]. If the role of diabetes and impaired fasting glucose in respiratory health is confirmed [42, 43], glucose and other metabolic biomarkers may represent a pathway through which impaired lung function is related to CVD and other chronic diseases.

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