

Obesity in Adults Is Associated With Reduced Lung Function in Metabolic Syndrome and Diabetes

The Strong Heart Study

FAWN YEH, PHD¹
ANNE E. DIXON, MD²
SUSAN MARION, PHD³
CARL SCHAEFFER, PHD¹
YING ZHANG, PHD¹

LYLE G. BEST, MD⁴
DARREN CALHOUN, PHD⁵
EVERETT R. RHOADES, MD¹
ELISA T. LEE, PHD¹

OBJECTIVE—The purposes of this study were to investigate whether reduced lung function is associated with metabolic syndrome (MS) and diabetes (DM) in American Indians (AIs) and to determine whether lower pulmonary function presents before the development of DM or MS.

RESEARCH DESIGN AND METHODS—The Strong Heart Study (SHS) is a multicenter, prospective study of cardiovascular disease (CVD) and its risk factors among AI adults. The present analysis used lung function assessment by standard spirometry at the SHS second examination (1993–1995) in 2,396 adults free of overt lung disease or CVD, with or without DM or MS. Among MS-free/DM-free participants, the development of MS/DM at the SHS third examination (1996–1999) was investigated.

RESULTS—Significantly lower pulmonary function was observed for AIs with MS or DM. Impaired pulmonary function was associated with MS and DM after adjustment for age, sex, abdominal obesity, current smoking status, physical activity index, hypertension, and SHS field center. Both forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were negatively associated with insulin resistance or DM severity and with serum markers of inflammation ($P < 0.05$). FVC and FEV1-to-FVC ratio both predicted DM in unadjusted analyses but not when adjusted for covariates, including waist circumference. In the adjusted model, abdominal obesity predicted both MS and DM.

CONCLUSIONS—Reduced lung function is independently associated with MS and with DM, and impaired lung function presents before the development of MS or DM; these associations may result from the effects of obesity and inflammation.

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Pulmonary dysfunction has been reported in type 2 diabetes (T2DM) (1–4), and prospective studies suggest that reduced lung function may be associated with the development of diabetes (DM) and inflammation may contribute to incident DM (5,6); however, the underlying mechanism remains unclear. Studies also indicate a possible association among obesity, metabolic syndrome

(MS), and pulmonary impairment in a restrictive pattern (7–9), but no study of lung function has included both DM and MS.

American Indians (AIs) have the highest prevalence of DM of any segment of the U.S. population (10). The aims of this study were to test the hypotheses that reduced lung function is independently associated with MS and DM and to test whether impaired lung function

presents before the development of MS or DM in AIs.

RESEARCH DESIGN AND METHODS

The Strong Heart Study (SHS) is a multicenter, population-based, prospective study of cardiovascular disease (CVD) and its risk factors among AI adults. The study design, survey methods, and laboratory techniques have been described previously (11,12). The study population is composed of tribal members who reside in study communities. The present analysis was based on the second examination and the 4-year follow-up clinic visit—the third examination. The second examination included 3,638 participants, and the third included 3,197. Approval was obtained from relevant institutional review boards, and all participants gave written informed consent.

The following criteria were used in excluding participants from the analysis population: 1) >20 pack-year smoking history ($n = 639$), 2) any self-reported lung problems and taking asthma medications ($n = 179$), 3) having CVD ($n = 430$), and 4) missing data on DM, MS status, or spirometry ($n = 268$). The final study sample consisted of 2,396 individuals, including 483 adults without MS or DM (normal group), 729 adults without DM and with MS (MS group), and 1,184 adults with DM (DM group) at the second examination. These three groups of participants were mutually exclusive. MS-free (483 normal) and DM-free (483 normal and 729 MS) participants were used for the prediction of MS and DM, respectively.

Pulmonary function tests

Spirometry was performed by centrally trained and certified nurses and technicians. Normal reference values for the pulmonary function test (PFT) were derived from the SHS population; SHS-specific forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were predicted using the equations developed by Marion et al. (13) for healthy SHS participants using the covariates of age, sex, and height. The

From the ¹Center for American Indian Health Research, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; the ²Pulmonary Disease & Critical Care Medicine Unit, College of Medicine, University of Vermont, Burlington, Vermont; the ³Department of Physical Therapy, University of Delaware, Newark, Delaware; ⁴Missouri Breaks Industries Research Inc., Timber Lake, South Dakota; and the ⁵MedStar Research Institute, Phoenix Field Office, Phoenix, Arizona.

Corresponding author: Fawn Yeh, fawn-yeh@ouhsc.edu.

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prediction equations for normal lung function for men are as follows:

$$FVC = 0.0807 \text{ height} - 0.0129 \text{ age} - 8.840$$

$$FEV1 = 0.0599 \text{ height} - 0.0240 \text{ age} - 5.650$$

$$FEV1/FVC\% = -0.328 \text{ age} + 94.789$$

The prediction equations for normal lung function for women are as follows:

$$FVC = 0.0490 \text{ height} - 0.0258 \text{ age} - 3.208$$

$$FEV1 = 0.0358 \text{ height} - 0.0262 \text{ age} - 1.774$$

$$FEV1/FVC\% = -0.1967 \text{ age} + 89.565$$

Before the analysis, crude data on FVC and FEV1 were divided by predicted FVC and FEV1, respectively, to yield FVC % predicted and FEV1 % predicted.

DM

Individuals were classified as having DM according to the 1997 American Diabetes

Association criteria; a fasting glucose level of at least 7.0 mmol/L (126 mg/dL); current use of antidiabetes medication; or on renal dialysis/kidney transplant with a positive response to the question, "Has a medical person ever told you that you had diabetes?" This group included both T1DM and T2DM; the majority of the participants were T2DM.

MS

MS was defined according to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines (14) as having at least three of the following five conditions: abdominal obesity (waist circumference [WC] >102 cm in men and >88 cm in women), increased triglycerides (≥ 150 mg/dL), reduced HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women), elevated blood pressure ($\geq 130/\geq 85$ mmHg), and high fasting glucose (100–125 mg/dL).

Other variables

The definitions and methods used for other measurements (age, education level, cigarette smoking status and pack-years of smoking, physical activity index, height, BMI, and hypertension) have been reported previously (12,15). The methods used for the measurement of fibrinogen and C-reactive protein (CRP) were also reported before (16). The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated according to the following formula: (fasting insulin in $\mu\text{U/mL} \times$ fasting glucose in mg/dL)/405.

Data analysis

Characteristics of normal, MS, and DM groups were compared using ANOVA for continuous variables and χ^2 tests for categorical variables. Kruskal-Wallis ANOVA by ranks was used to compare total triglycerides, plasminogen activator inhibitor-1, and CRP because of skewed distributions.

Multiple linear regression models were used to describe the cross-sectional

Table 1—Demographic information for normal, MS, and DM groups

	Normal (n = 483)	MS (n = 729)	DM (n = 1,184)	P value*
Arizona	96	231	615	
Oklahoma	205	273	312	
North and South Dakota	182	225	257	
Male	226	233	340	
Female	257	496	844	
Mean age (years)	59.1 (8.1)	59.6 (8.1)	59.5 (7.6)	0.5819
High school graduate (%)	57.2 (52.8–61.6)	59.3 (55.7–62.9)	48.6 (45.8–51.5)	<0.0001
Cigarette smoking (%)				
Current smoker	35.3 (30.9–39.6)	24.0 (20.9–27.2)	21.4 (19.0–23.8)	<0.0001
Ex-smoker	32.5	39.2	41.1	
Never smoker	32.3	36.8	37.5	
Pack-years of smoking‡	4.6 (5.9)	3.8 (5.7)	3.1 (4.9)	<0.0001
Leisure activity in past year (MET hours per week)	32.7 (47.0)	26.7 (41.2)	22.5 (36.6)	<0.0001
WC (cm)	98.2 (12.8)	109.5 (13.4)	110.9 (14.2)	<0.0001
BMI (kg/m ²)	27.3 (5.2)	32.7 (6.0)	32.8 (6.5)	<0.0001
Hypertension (%)	23.4 (19.6–27.2)	43.8 (40.2–47.4)	56.1 (53.3–58.9)	<0.0001
LDL cholesterol (mg/dL)	116.9 (33.4)	122.0 (33.5)	114.5 (32.7)	<0.0001
Total triglyceride (mg/dL)§	92 (67, 119)	142 (100, 193)	145 (103, 206)	<0.0001
Hemoglobin A _{1c} (%)	5.2 (0.9)	5.4 (0.9)	8.7 (2.3)	<0.0001
Pai 1 (ng/mL)§	32.0 (21.0, 50.0)	46.0 (31.0, 69.0)	46.0 (31.0, 69.0)	<0.0001
Fibrinogen (mg/dL)	329.6 (65.2)	344.9 (64.8)	383.9 (90.3)	<0.0001
CRP (mg/L)§	2.6 (1.4, 4.9)	3.6 (2.0, 6.5)	4.3 (2.4, 8.3)	<0.0001
Albuminuria (%)				
Macroalbuminuria	2.3 (1.0–3.7)	2.9 (1.7–4.2)	23.1 (20.7–25.6)	<0.0001
Microalbuminuria	11.6	11.7	34.2	
No albuminuria	86.1	85.4	42.7	
FEV1-to-FVC ratio (%)	74.8 (8.9)	76.3 (7.1)	77.2 (8.1)	<0.0001
FVC % predicted (%)	99.4 (17.1)	94.5 (16.5)	90.3 (17.7)	<0.0001
FEV1 % predicted (%)	96.9 (17.2)	93.8 (17.0)	90.1 (16.6)	<0.0001

Data in parentheses are 1 SD for continuous variables and 95% CI for percentages unless otherwise indicated. MET, metabolic equivalent; Pai 1, plasminogen activator inhibitor-1. *For continuous variables, analyses of variance were used to calculate the P values; for categorical variables, χ^2 tests were used to calculate the P values. ‡For current and ex-smokers only. §Median, first quartile, and third quartile.

relationships between lung function and metabolic disorders (MS and DM) after adjusting for potential confounding variables including age, sex, abdominal obesity, height, hypertension, physical activity index, education level, current smoking status, and SHS center. The same models were also fitted to describe the cross-sectional associations among lung function and duration of DM, type of antidiabetes medications, and tertiles of insulin resistance after adjusting for potential confounding variables.

Multiple linear regression models were also used to describe the cross-sectional relationships between lung function and inflammatory markers (CRP and fibrinogen). For CRP analyses, participants with values >10 mg/L were excluded because CRP levels >10 mg/L may reflect an acute inflammatory process; CRP >3 mg/L was used as the high CRP cut point based on the American Heart Association/Centers for Disease Control and Prevention categories (17). For fibrinogen analyses, the lowest tertile of fibrinogen level in the normal group (≤ 350 mg/dL) was used as a control for the lung function comparisons. Multiple linear regression models were also carried out for investigation of the cross-sectional relationship between lung function and obesity. Cox proportional hazards models were used to analyze the association between DM/MS and pulmonary function, controlling for confounding variables. All tests of significance were two-tailed, with an α -level of 0.05. All analyses were performed using version 9.1 of the SAS statistical software package (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics

Characteristics of the three groups (normal, MS, and DM) are summarized in Table 1. Of the participants, 75.2% reported 100% AI heritage. There were no significant differences among these three groups for age. In general, participants with DM or MS were more likely to be hypertensive and smoked less than the normal group. They were also more likely to have a larger WC, higher triglycerides, lower HDL cholesterol, higher hemoglobin A_{1c}, presence of albuminuria, and an elevated concentration of inflammatory markers compared with the normal group. LDL cholesterol was higher in the MS group than in the normal and DM groups.

The clinical measurements of the excluded group because of missing DM,

Table 2—Adjusted spirometry results for normal, MS, and DM groups and by insulin resistance and DM severity

	FVC (mL)	FEV1 (mL)	FVC % predicted	FEV1 % predicted	FEV1-to-FVC ratio (%)
Normal	3,637 (3,573–3,701)	2,693 (2,642–2,743)	98.8 (97.1–100.6)	96.1 (94.4–97.9)	74.4 (73.6–75.2)
MS	3,513 (3,452–3,573)	2,613 (2,565–2,661)	95.9 (94.3–97.6)	93.8 (92.2–95.5)	74.7 (73.9–75.5)
DM	3,448 (3,396–3,500)	2,583 (2,542–2,624)	93.8 (92.4–95.3)	92.3 (90.9–93.7)	75.5 (74.9–76.2)
<i>P</i> _{trend} value†	<0.0001	0.0008	<0.0001	0.0009	0.0313
MS, by insulin resistance‡					
<3.6 vs. normal	–39 (–174 to 97)	–54 (–165 to 58)	–1.5 (–5.1 to 2.1)	–2.0 (–5.7 to 1.7)	–0.4 (–2.0 to 1.3)
3.6–5.8 vs. normal	–118 (–254 to 19)	–57 (–169 to 55)	–2.0 (–5.6 to 1.7)	–0.9 (–4.6 to 2.8)	0.7 (–1.0 to 2.3)
>5.8 vs. normal	–226 (–367 to –86)	–129 (–244 to –13)	–5.8 (–9.5 to –2.1)	–4.1 (–8.0 to –0.3)	1.1 (–0.6 to 2.8)
<i>P</i> _{trend} value†	<0.0001	0.0117	0.0005	0.0299	0.0617
DM, by duration (years)					
<5 vs. normal	–169 (–292 to –46)	–132 (–229 to –36)	–4.3 (–7.7 to –0.8)	–4.3 (–7.6 to –0.9)	0.2 (–1.4 to 1.8)
5–10 vs. normal	–179 (–305 to –53)	–106 (–206 to –7)	–4.6 (–8.1 to –1.0)	–3.7 (–7.1 to –0.2)	1.0 (–0.6 to 2.7)
>10 vs. normal	–217 (–337 to –97)	–128 (–222 to –34)	–5.4 (–8.8 to –2.1)	–4.3 (–7.5 to –1.0)	1.3 (–0.3 to 2.8)
<i>P</i> _{trend} value†	<0.0001	0.0055	0.0003	0.0062	0.0307
DM, by medications					
No medication vs. normal	–141 (–264 to –19)	–114 (–210 to –18)	–3.6 (–7.1 to –0.2)	–4.1 (–7.5 to –0.8)	0.0 (–1.6 to 1.6)
Oral agents vs. normal	–181 (–298 to –64)	–101 (–193 to –9)	–3.8 (–7.1 to –0.6)	–2.4 (–5.6 to 0.8)	1.4 (–0.2 to 2.9)
Insulin (alone or with oral) vs. normal	–254 (–379 to –129)	–162 (–260 to –64)	–7.3 (–10.8 to –3.8)	–6.3 (–9.7 to –2.9)	1.0 (–0.6 to 2.6)
<i>P</i> _{trend} value†	<0.0001	0.0003	<0.0001	0.0002	0.0494
DM, by insulin resistance‡					
<8.5 vs. normal	–155 (–274 to –36)	–127 (–220 to –33)	–3.6 (–6.9 to –0.2)	–3.8 (–7.0 to –0.5)	–0.1 (–1.7 to 1.4)
8.5–14.8 vs. normal	–150 (–272 to –27)	–70 (–166 to 27)	–3.7 (–7.1 to –0.3)	–2.4 (–5.8 to 1.0)	1.4 (–0.2 to 3.0)
>14.8 vs. normal	–261 (–385 to –136)	–160 (–258 to –62)	–7.0 (–10.5 to –3.5)	–5.7 (–9.1 to –2.3)	1.5 (–0.1 to 3.1)
<i>P</i> _{trend} value†	<0.0001	0.0016	<0.0001	0.0008	0.0073

Data are means (95% CI) adjusted for age, sex, abdominal obesity, height, hypertension, physical activity index, education level, current smoking status, and SHS center. †*P* values correspond to tests for linear trend across categories. ‡Insulin resistance was measured by HOMA.

Table 3—Adjusted spirometry results for normal, MS, and DM groups by inflammatory markers

	FVC (mL)	FEV1 (mL)	FVC % predicted	FEV1 % predicted	FEV1-to-FVC ratio (%)
CRP					
Normal					
Low CRP	3,652 (3,549–3,756)	2,707 (2,622–2,792)	99.1 (96.5–101.6)	96.7 (94.1–99.3)	74.4 (73.1–75.7)
High CRP†	3,541 (3,421–3,662)	2,576 (2,477–2,675)	96.8 (93.8–99.8)	92.3 (89.2–95.3)	72.7 (71.2–74.2)
High CRP vs. low CRP	–111 (–245 to 23)	–131 (–241 to –21)	–2.3 (–5.6 to 1.1)	–4.4 (–7.8 to –1.0)	–1.7 (–3.3 to 0)
P value	0.1043	0.0198	0.1835	0.0111	0.0521
MS					
Low CRP vs. normal, low CRP	–130 (–253 to –6)	–82 (–181 to 16)	–3.5 (–6.9 to –0.2)	–3.5 (–6.9 to –0.1)	0.2 (–1.3 to 1.7)
High CRP vs. normal, low CRP	–261 (–384 to –138)	–135 (–233 to –37)	–7.5 (–10.8 to –4.2)	–5.2 (–8.5 to –1.8)	1.5 (0 to 2.9)
P _{trend} value‡	<0.0001	0.0024	<0.0001	0.0007	0.0315
DM					
Low CRP vs. normal, low CRP	–211 (–335 to –87)	–109 (–205 to –14)	–4.7 (–8.2 to –1.2)	–3.2 (–6.5 to 0.2)	1.4 (–0.2 to 3.0)
High CRP vs. normal, low CRP	–254 (–372 to –136)	–164 (–254 to –73)	–7.4 (–10.7 to –4.1)	–6.7 (–9.9 to –3.5)	0.8 (–0.7 to 2.3)
P _{trend} value‡	<0.0001	<0.0001	<0.0001	<0.0001	0.2345
FIB					
Normal					
Low FIB	3,640 (3,539–3,740)	2,704 (2,622–2,785)	98.7 (96.1–101.3)	96.6 (94.0–99.2)	74.6 (73.3–75.9)
High FIB§	3,612 (3,492–3,732)	2,631 (2,534–2,728)	98.4 (95.3–101.6)	93.6 (90.6–96.7)	72.8 (71.2–74.3)
High FIB vs. low FIB	–28 (–163 to 107)	–73 (–182 to 37)	–0.3 (–3.8 to 3.3)	–3.0 (–6.4 to 0.5)	–1.8 (–3.5 to –0.1)
P value	0.6833	0.1928	0.8840	0.0929	0.0415
MS					
Low FIB vs. normal, low FIB	–154 (–266 to –42)	–73 (–163 to 17)	–4.7 (–7.7 to –1.7)	–3.7 (–6.7 to –0.6)	0.8 (–0.5 to 2.1)
High FIB vs. normal, low FIB	–208 (–331 to –85)	–130 (–228 to –32)	–5.9 (–9.2 to –2.7)	–5.0 (–8.4 to –1.7)	0.5 (–0.9 to 2.0)
P _{trend} value‡	0.0002	0.0036	<0.0001	0.0009	0.4108
DM					
Low FIB vs. normal, low FIB	–178 (–290 to –67)	–100 (–186 to –14)	–4.3 (–7.4 to –1.2)	–3.7 (–6.8 to –0.7)	1.1 (–0.3 to 2.5)
High FIB vs. normal, low FIB	–295 (–407 to –182)	–181 (–268 to –95)	–8.7 (–11.8 to –5.5)	–7.3 (–10.3 to –4.2)	1.1 (–0.4 to 2.5)
P _{trend} value‡	<0.0001	0.0001	<0.0001	<0.0001	0.1004

Data are means (95% CI) adjusted for age, sex, height, hypertension, physical activity index, education level, current smoking status, and SHS center. FIB, fibrinogen. †High CRP was defined as CRP >3.0 mg/L. ‡P values correspond to tests for linear trend across categories. §High fibrinogen was defined as plasma fibrinogen >350 mg/dL.

MS, or PFT status were similar to those of the study group, with the exception that they were more likely to have smaller WCs (data not shown).

Pulmonary function in normal, MS, and DM groups

Both percent predicted values for FVC and FEV1 were significantly lower in the participants with MS or DM compared with their normal counterparts ($P < 0.0001$) (Table 1), even after adjusting for age, sex, abdominal obesity, height, hypertension, sports activity index, education level, current smoking status, and SHS center (Table 2). An increased trend for MS and DM was observed for the FEV1-to-FVC ratio.

Significant relationships were found among pulmonary function and insulin resistance, duration of DM, and antidiabetes medications. Participants with higher HOMA-IR scores had greater reductions in both predicted FVC and FEV1 values ($P_{\text{trend}} < 0.05$) (Table 2). Subdividing the participants by duration of DM revealed that absolute and percent predicted FVC decreased with duration of DM ($P_{\text{trend}} < 0.01$). However, the reductions of FEV1 values were not different for durations < 5 years vs. > 10 years. Subdividing the participants by antidiabetes medications revealed that pulmonary

function was significantly reduced in participants requiring insulin treatment compared with those on oral agents alone or no medication ($P_{\text{trend}} < 0.01$). The relatively greater reduction in FVC than in FEV1 in DM participants with longer duration or more severe DM was reflected in the FEV1-to-FVC ratio.

Pulmonary function and inflammatory markers

Partitioning normal, MS, and DM participants according to blood levels of the inflammatory markers CRP and fibrinogen revealed that pulmonary function decreased as marker concentration increased (Table 3). Compared with normal participants, MS and DM groups with elevated inflammatory markers had greater reductions in their PFT (FVC, FEV1, FVC % predicted, and FEV1 % predicted all $P_{\text{trend}} < 0.01$).

Prediction of DM and MS

Among 1,212 participants who were DM-free at the SHS second examination, 129 developed DM during the 4 years of follow-up. By use of Cox proportional hazards models, in unadjusted analyses with FVC, FVC % predicted, FEV1, FEV1 % predicted, and FEV1-to-FVC ratio as continuous independent variables, FVC % predicted and FEV1-to-FVC ratio both predicted DM (Table 4, model 2). The risk

of incident DM increased 3% for every 1% increase in FEV1-to-FVC ratio (hazard ratio 1.03 [95% CI 1.01–1.06]), and the risk of incident DM increased 2% for every 1% decrease in FVC % predicted (0.98 [0.97–0.99]). The same results were obtained when age, sex, and SHS center were added to the model as covariates (model 3). However, when more covariates (abdominal obesity, hypertension, physical activity index, education level, and pack-years of smoking) were added to the Cox proportional hazards model, pulmonary function did not predict DM (Table 4, model 4); abdominal obesity, as measured by WC, was retained in the final model as an independent predictor of the development of DM.

Similar analyses of data from participants who developed MS indicated that FEV1-to-FVC ratio predicted DM; however, neither FVC nor FEV1 alone predicted this syndrome. As before, abdominal obesity was retained in the final model as an independent predictor for MS (Table 4).

Pulmonary function and obesity

Further investigation of obesity showed a significant reduction in pulmonary function in obese participants measured either by WC or by BMI (Table 5). Compared with normal participants, MS and DM adults with obesity had greater reductions

Table 4—Cox proportional hazards models for the prediction of DM or MS based on PFTs

Model	Variable	Hazard ratio	95% CI	P value	Covariate
For the prediction of DM					
1a	FVC	0.81	0.67–0.98	0.0263	Unadjusted model for every individual PFT
1b	FEV1	0.87	0.68–1.10	0.2373	
1c	FEV1-to-FVC ratio	1.04	1.01–1.07	0.0024	
1d	FVC % predicted	0.98	0.97–0.99	0.0009	
1e	FEV1 % predicted	0.99	0.98–1.00	0.0761	
2	FEV1-to-FVC ratio	1.03	1.01–1.06	0.0084	Unadjusted model for stepwise selection of PFTs
	FVC % predicted	0.98	0.97–0.99	0.0029	
3	FEV1-to-FVC ratio	1.03	1.01–1.06	0.0084	*
	FVC % predicted	0.98	0.97–0.99	0.0029	
4	None				Abdominal obesity†
For the prediction of MS					
1a	FVC	1.01	0.84–1.21	0.9126	Unadjusted model for every individual PFT
1b	FEV1	1.19	0.95–1.50	0.1372	
1c	FEV1-to-FVC ratio	1.03	1.01–1.06	0.0062	
1d	FVC % predicted	0.99	0.98–1.00	0.0862	
1e	FEV1 % predicted	1.00	0.99–1.01	0.8484	
2	FEV1-to-FVC ratio	1.03	1.01–1.06	0.0062	Unadjusted model for stepwise selection of PFTs
3	FEV1-to-FVC ratio	1.03	1.01–1.06	0.0062	
4	FEV1-to-FVC ratio	1.06	1.02–1.10	0.0013	Abdominal obesity†

*The model was reduced by stepwise selection. The covariates considered in the model were age, sex, and SHS center. All covariates were candidates for removal. Only those covariates that remained significant ($P \leq 0.05$) are shown in the table. †The model was reduced by stepwise selection. Pulmonary function was forced into the model. The covariates considered in the model were age, sex, abdominal obesity, hypertension, per pack-year smoking, physical activity index, education level, and SHS center. Only those covariates that remained significant ($P \leq 0.05$) are shown in the table.

Table 5—Adjusted spirometry results for normal, MS, and DM groups by obesity status

	FVC (mL)	FEV1 (mL)	FVC % predicted	FEV1 % predicted	FEV1-to-FVC ratio (%)
AO*					
Normal					
No AO	3,688 (3,590-3,794)	2,670 (2,583-2,757)	101.7 (99.0-104.5)	96.6 (93.8-99.3)	72.6 (71.3-74.0)
AO	3,564 (3,447-3,680)	2,695 (2,600-2,791)	95.2 (92.2-98.2)	94.6 (91.6-97.6)	75.6 (74.1-77.1)
AO vs. no AO	-124 (-266 to 18)	25 (-92 to 142)	-6.6 (-10.2 to -2.9)	-2.0 (-5.7 to 1.7)	3.0 (1.2-4.8)
P value	0.0867	0.6709	0.0005	0.2938	0.0013
MS					
No AO vs. normal, no AO	-134 (-350 to 82)	-34 (-207 to 139)	-4.1 (-9.9 to 1.6)	-1.5 (-7.3 to 4.4)	1.7 (-0.9 to 4.3)
AO vs. normal, no AO	-285 (-408 to -163)	-109 (-207 to -10)	-9.7 (-13.0 to -6.4)	-5.8 (-9.1 to -2.5)	2.6 (1.1-4.1)
P trend value‡	<0.0001	0.0142	<0.0001	0.0001	0.0001
DM					
No AO vs. normal, no AO	-191 (-358 to -23)	-84 (-214 to 46)	-4.4 (-9.1 to 0.3)	-2.6 (-7.2 to 1.9)	1.6 (-0.6 to 3.8)
AO vs. normal, no AO	-328 (-447 to -210)	-134 (-226 to -42)	-10.2 (-13.5 to -6.9)	-6.2 (-9.4 to -3.0)	3.1 (1.6-4.7)
P trend value‡	<0.0001	0.0012	<0.0001	<0.0001	<0.0001
OBS§					
Normal					
No OBS	3,665 (3,573-3,757)	2,682 (2,606-2,758)	100.3 (97.9-102.7)	96.3 (93.9-98.7)	73.3 (72.1-74.5)
OBS	3,536 (3,398-3,674)	2,679 (2,566-2,793)	94.3 (90.7-97.9)	93.9 (90.3-97.4)	75.8 (74.0-77.5)
OBS vs. no OBS	-129 (-273 to 15)	-2 (-121 to 116)	-6.0 (-9.8 to -2.3)	-2.5 (-6.2 to 1.3)	2.4 (0.6-4.3)
P value	0.0795	0.9702	0.0016	0.1916	0.0096
MS					
No OBS vs. normal, no OBS	-153 (-281 to -25)	-61 (-165 to 43)	-6.2 (-9.7 to -2.8)	-4.1 (-7.6 to -0.6)	1.2 (-0.4 to 2.8)
OBS vs. normal, no OBS	-276 (-386 to -165)	-120 (-210 to -31)	-8.4 (-11.4 to -5.4)	-5.2 (-8.2 to -2.2)	2.2 (0.9-3.6)
P trend value‡	<0.0001	0.0030	<0.0001	0.0002	0.0003
DM					
No OBS vs. normal, no OBS	-229 (-344 to -113)	-117 (-207 to -27)	-6.7 (-10.0 to -3.5)	-4.7 (-7.9 to -1.6)	1.5 (0-3.0)
OBS vs. normal, no OBS	-308 (-413 to -203)	-142 (-224 to -60)	-9.4 (-12.4 to -6.5)	-6.3 (-9.2 to -3.4)	2.7 (1.3-4.0)
P trend value‡	<0.0001	0.0002	<0.0001	<0.0001	<0.0001

Data are means (95% CI) adjusted for age, sex, height, hypertension, physical activity index, education level, current smoking status, and SHS center. AO, abdominal obesity; OBS, obesity. * AO was defined as WC >102 cm in men and >88 cm in women. ‡P values correspond to tests for linear trend across categories. §OBS was defined as BMI ≥30 kg/m².

in their PFT (FVC, FEV1, FVC % predicted, and FEV1 % predicted all $P_{\text{trend}} < 0.05$).

CONCLUSIONS

Pulmonary function, MS, and DM

In this study, adult AIs with MS or DM had significantly lower FVC, FEV1, FVC % predicted, and FEV1 % predicted compared with normal AI participants. This relationship persisted after adjustment for multiple factors, including obesity, and was related to metabolic disorders and markers of inflammation. Major strengths of the current study are the inclusion of multiple measures of metabolic disorders and the consistency of the results for all these measurements. Our results are also consistent with those of other studies (7–9) that show restrictive lung function (reduced FVC and increased FEV1-to-FVC ratio), but not obstructive pulmonary function (decreased FEV1-to-FVC ratio), to be associated with MS and DM.

Participants with MS had significantly lower FVC, FEV1, FVC % predicted, and FEV1 % predicted compared with participants without DM or MS. These relationships were graded by insulin resistance. Our results are consistent with cross-sectional studies (7,8,18).

In patients with DM, the relationships were graded by DM severity and serum markers of inflammation after the adjustment for possible confounders. Our results support cross-sectional studies, which demonstrate lower FVC and FEV1 in adults with DM compared with their nondiabetic counterparts (1,19,20), especially when DM was of longer duration and subjects required medication treatment (1), had a higher HOMA score (19) and had higher levels of serum inflammatory markers (21).

Obesity is associated with pulmonary function and DM

Previous studies suggest that impaired lung function predicts the subsequent development of clinical DM (5,6); studies also show that WC predicts DM beyond commonly evaluated cardiometabolic risk factors (22,23). Yet few studies have assessed whether the relationship between lung function and DM is mediated by central obesity. Leone et al. (18) found that the relationship between lung function impairment and MS was predominantly due to abdominal obesity; our data also suggest that abdominal obesity is a significant factor that affects MS, DM, and PFT.

The underlying mechanisms relating this type of metabolic disorder to reduced lung function remain unclear; integration of inflammatory and metabolic pathways in MS or DM patients may be an important underlying mechanism relating the disorders to reduced lung function (24).

In the current study, there was a significant, graded, and inverse relationship between PFT and WC and/or BMI, indicating that obesity played a significant role in the relationship of reduced PFT and metabolic disorders. There was also a significant, graded, and inverse relationship between lung function and inflammatory markers, indicating that inflammation played a significant role in the relationship of reduced PFT and metabolic disorders. These observations seem to support the suggested mediatory mechanisms of inflammation and obesity.

The strengths of this study include the community-based sample, standardized spirometric techniques, extensive data on potential confounders, and a large sample size that increased precision and permitted multiple statistical adjustments. The study's limitations include lack of generalizability of results to heavy/prolonged smokers and the lack of data on obesity-related inflammatory markers, which precluded more detailed investigations of the causal pathway.

The main conclusions from the cross-sectional analyses are that reduced lung function is independently associated with MS and DM and that obesity and inflammation are associated with reduced lung function in MS and DM; impaired lung function presents before the development of MS or DM in AIs. Further studies are needed to investigate how inflammation and obesity affect lung function in patients with MS and DM.

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F.Y. wrote the manuscript. A.E.D. contributed to discussion and reviewed and edited the manuscript. S.M. researched data and reviewed and edited the manuscript. C.S., Y.Z., L.G.B., and D.C. contributed to discussion and reviewed and edited the manuscript. E.R.R. researched data and reviewed and edited the manuscript. E.T.L. contributed to discussion and reviewed and edited the manuscript.

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References

1. Yeh HC, Punjabi NM, Wang NY, et al. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care* 2008;31:741–746
2. Wannamethee SG, Shaper AG, Rumley A, et al. Lung function and risk of type 2 diabetes and fatal and nonfatal major coronary heart disease events: possible associations with inflammation. *Diabetes Care* 2010;33:1990–1996
3. Klein OL, Krishnan JA, Glick S, Smith LJ. Systematic review of the association between lung function and type 2 diabetes mellitus. *Diabet Med* 2010;27:977–987
4. van den Borst B, Gosker HR, Zeegers MP, Schols AMW. Pulmonary function in diabetes: a metaanalysis. *Chest* 2010;138:393–406
5. Ford ES, Mannino DM; National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Prospective association between lung function and the incidence of diabetes: findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Diabetes Care* 2004;27:2966–2970
6. Yeh HC, Punjabi NM, Wang NY, Pankow JS, Duncan BB, Brancati FL. Vital capacity as a predictor of incident type 2 diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care* 2005;28:1472–1479
7. Lin WY, Yao CA, Wang HC, Huang KC. Impaired lung function is associated with obesity and metabolic syndrome in adults. *Obesity (Silver Spring)* 2006;14:1654–1661
8. Nakajima K, Kubouchi Y, Muneyuki T, Ebata M, Eguchi S, Munakata H. A possible association between suspected restrictive pattern as assessed by ordinary pulmonary function test and the metabolic syndrome. *Chest* 2008;134:712–718
9. Fimognari FL, Pasqualetti P, Moro L, et al. The association between metabolic syndrome and restrictive ventilatory dysfunction in older persons. *J Gerontol A Biol Sci Med Sci* 2007;62:760–765
10. Centers for Disease Control and Prevention. National diabetes fact sheet, 2007

- [article online], 2007. Available from http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf. Accessed 15 June 2011
11. Lee ET, Welty TK, Fabsitz R, et al. The Strong Heart Study. A study of cardiovascular disease in American Indians: design and methods. *Am J Epidemiol* 1990; 132:1141–1155
 12. Howard BV, Welty TK, Fabsitz RR, et al. Risk factors for coronary heart disease in diabetic and nondiabetic Native Americans. The Strong Heart Study. *Diabetes* 1992;41(Suppl. 2):4–11
 13. Marion MS, Leonardson GR, Rhoades ER, Welty TK, Enright PL. Spirometry reference values for American Indian adults: results from the Strong Heart Study. *Chest* 2001;120:489–495
 14. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109:433–438
 15. Welty TK, Lee ET, Yeh J, et al. Cardiovascular disease risk factors among American Indians: the Strong Heart Study. *Am J Epidemiol* 1995;142:269–287
 16. Best LG, Zhang Y, Lee ET, et al. C-reactive protein as a predictor of cardiovascular risk in a population with a high prevalence of diabetes: the Strong Heart Study. *Circulation* 2005;112:1289–1295
 17. Pearson TA, Mensah GA, Alexander RW, et al.; Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499–511
 18. Leone N, Courbon D, Thomas F, et al. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med* 2009; 179:509–516
 19. Lawlor DA, Ebrahim S, Smith GD. Associations of measures of lung function with insulin resistance and type 2 diabetes: findings from the British Women's Heart and Health Study. *Diabetologia* 2004;47: 195–203
 20. Davis WA, Knuiiman M, Kendall P, Grange V, Davis TME; Fremantle Diabetes Study. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care* 2004;27:752–757
 21. Dennis RJ, Maldonado D, Rojas MX, et al. Inadequate glucose control in type 2 diabetes is associated with impaired lung function and systemic inflammation: a cross-sectional study. *BMC Pulm Med* 2010; 10:38
 22. Janiszewski PM, Janssen I, Ross R. Does waist circumference predict diabetes and cardiovascular disease beyond commonly evaluated cardiometabolic risk factors? *Diabetes Care* 2007;30:3105–3109
 23. McClean KM, Kee F, Young IS, Elborn JS. Obesity and the lung: 1. Epidemiology. *Thorax* 2008;63:649–654
 24. Shore SA. Obesity, airway hyperresponsiveness, and inflammation. *J Appl Physiol* 2010;108:735–743