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 Schaefer, PhD1
Ying Zhang, PhD1
Lyie G. Best, MD4
Darren Calhoun, PhD5
Everett R. Rhodes, 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 DM, and impaired lung function presents before the development of MS or DM; these associations may result from the effects of obesity and inflammation.

Diabetes Care 34:2306–2313, 2011

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
prediction equations for normal lung function for men are as follows:
\[
\text{FVC} = 0.0807 \times \text{height} - 0.0129 \times \text{age} - 8.840 \\
\text{FEV1} = 0.0599 \times \text{height} - 0.0240 \times \text{age} - 5.650 \\
\text{FEV1/FVC} = -0.328 \times \text{age} + 94.789
\]
The prediction equations for normal lung function for women are as follows:
\[
\text{FVC} = 0.0490 \times \text{height} - 0.0258 \times \text{age} - 3.208 \\
\text{FEV1} = 0.0358 \times \text{height} - 0.0262 \times \text{age} - 1.774 \\
\text{FEV1/FVC} = -0.1967 \times \text{age} + 89.565
\]
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 (≥130/≥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 µU/mL × fasting glucose in mg/dL)/405.

**Data analysis**

Characteristics of normal, MS, and DM groups were compared using ANOVA for continuous variables and χ² 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 (32.8–61.6) | 59.3 (53.7–62.9) | 48.6 (45.8–51.5) | <0.0001 |
| 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 (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/m²)     | 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 A₁c (%) | 5.2 (0.9)   | 5.4 (0.9)   | 8.7 (2.3)     | <0.0001 |
| Pai 1 (mg/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/dL)‡ | 2.6 (1.4, 4.9)   | 3.6 (2.0, 6.5) | 4.3 (2.4, 8.3) | <0.0001 |
| Albuminuria (%) |                 |             |               |         |
| Microalbuminuria| 2.3 (1.0–3.7)   | 2.9 (1.7–4.2) | 23.1 (20.7–25.6) | <0.0001 |
| No albuminuria  | 11.6             | 11.7        | 34.2          |         |
| 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, χ² tests were used to calculate the P values. ‡For current and ex-smokers only. §Median, first quartile, and third quartile.
**RESULTS**

**Baseline characteristics**

Characteristics of the three groups (normal, MS, and DM) are summarized in Table 1. Of the participants, 75.2% reported 10% or more for age. There were no significant differences for age, gender, or smoking status between the groups. Participants in the normal group were more likely to be hypertensive and smoked less than the normal group. There were no significant differences for age among these three groups. DM or MS were more likely to be hypertensive and smoked less than the normal group. However, HDL cholesterol was higher in the MS group compared to the normal group. Reduced lung function in adults with diabetes was associated with diabetes duration and duration of antidiabetes medications.

Multiple linear regression models were used as the control for the lung function comparisons. Multiple linear regression models were used to describe the cross-sectional relationship between lung function and inflammatory markers (CRP and fibrinogen) (17). For fibrinogen analyses, the lowest tertile of fibrinogen (≤50 mg/dL) was used as the reference point. CRP >3 mg/L was used as the high CRP cut point based on fitness, age, sex, abdominal obesity, hypertension, physical activity index, education level, smoking status, and SHS (Systolic Blood Pressure) score. The trend values correspond to tests for linear trend across categories.

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

| Category                | 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) |
| **P-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) |
| 3.6–5.5 vs. normal      | −118 (−254 to 19) | −57 (−165 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) |
| **P-trend value**‡       | <0.0001  | 0.0117    | 0.0005          | 0.0299           | 0.0617                |
| DM by duration (years)  |         |           |                 |                  |                       |
| <5 vs. normal           | −160 (−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) |
| **P-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) |
| **P-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) |
| **P-trend value**‡       | <0.0001  | 0.0016    | <0.0001         | 0.0008           | 0.073                 |

Data are means (95% CI) adjusted for age, sex, abdominal obesity, 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 associations results for normal, MS, and DM groups by inflammation markers.

| CRP (mg/L) | FVC (mL) | FEV1 (mL) | FEV1 % predicted | FVC % predicted |
|-----------|----------|-----------|------------------|-----------------|
| Normal    |          |           |                  |                 |
| High CRP  |          |           |                  |                 |
| Low CRP   |          |           |                  |                 |
| High FIB  |          |           |                  |                 |
| Low FIB   |          |           |                  |                 |
| DM        |          |           |                  |                 |
| MS        |          |           |                  |                 |

Data are means (95% CI) adjusted for age, sex, height, hypertension, physical activity index, education level, current smoking status, and SHS center. FIB, fibrinogen; CRP, C-reactive protein; DM, diabetes mellitus; MS, multiple sclerosis.
Reduced lung function in adults with diabetes

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 for the prediction of DM | 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 |
| 3                             | FVC % predicted | 0.98 | 0.97–0.99 | 0.0029 |           |
| 4                             | None     | 0.98         | 0.97–0.99 | 0.0029 |           |

| 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)                  | FEV1 % predicted | FVC % predicted | FEV1/ FVC ratio (%) | FEV1 (mL) | FVC (mL) |
|----------------|---------------------------|----------------------------|------------------|-----------------|---------------------|-----------|----------|
| **AO* Normal** | 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 Normal**  | 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** | 2124 (2266 to 18)        | 25 (292 to 142)            | 26.6 (210 to 29.2)| 2.0 (5.7 to 1.7) | 3.0 (1.2–4.8)       |           |          |
| **P value**    | 0.0867                    |                            |                  |                 |                     |           |          |
| **AO MS**      | 3,134 (3,350–2,23)        | 2,34 (2,207 to 139)        | 24.1 (29.9 to 1.6)| 1.5 (7.3 to 4.4) | 1.7 (0.9 to 3.8)    |           |          |
| **AO vs. no AO** | 285 (408 to 216)        | 109 (226 to 42)            | 9.7 (13.5 to 6.4) | 2.6 (9.1 to 2.5) | 2.6 (1.1–4.1)       |           |          |
| **P value**    | 0.0001                    |                            |                  |                 |                     |           |          |
| **AO DM**      | 2,191 (2,358–2,23)        | 2,84 (2,214 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. 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 value**    | 0.0013                    |                            |                  |                 |                     |           |          |

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

**OBS was defined as BMI $\geq 30$ 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/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.

**Acknowledgments**—The SHS was supported by cooperative agreements U01-HL41642, U01-HL41652, and U01-HL41654 from the National Institutes of Health National Heart, Lung, and Blood Institute.

No potential conflicts of interest relevant to this article were reported.

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.

**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;33:1900–1906

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

Parts of this study were presented in poster form at the 70th Scientific Sessions of the American Diabetes Association, Orlando, Florida, 25–29 June 2010.

The authors acknowledge the assistance and cooperation of the participating tribes and the Indian Health Service facilities serving those tribes. The authors also thank the study participants and the directors of the SHS clinics and their staff.
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 JL, 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, Knuiman 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