Vital Capacity as a Predictor of Incident Type 2 Diabetes

The Atherosclerosis Risk in Communities study

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OBJECTIVE — To test the hypothesis that lower vital capacity is cross-sectionally associated with features of insulin resistance and is an independent predictor of incident type 2 diabetes.

RESEARCH DESIGN AND METHODS — We conducted a prospective cohort study of vital capacity as a predictor of incident type 2 diabetes using 9-year follow-up data on 11,479 middle-aged adults without diabetes at baseline from the Atherosclerosis Risk in Communities (ARIC) Study.

RESULTS — Forced vital capacity (FVC) and forced expiratory volume in 1 s were measured at baseline using standard spirometry. Incident type 2 diabetes cases were ascertained during follow-up. At baseline, low FVC (% predicted) was independently associated with indicators of the insulin resistance syndrome, including higher fasting levels of glucose, insulin, and triglycerides; lower fasting HDL cholesterol; and higher systolic blood pressure. In prospective analyses, there were graded associations between low FVC (% predicted) and incidence of type 2 diabetes in men and women. These associations persisted in multivariable analyses that adjusted for age, race, adiposity, smoking, physical activity, and ARIC center. Compared with individuals in the highest quartile of FVC (% predicted), the fully adjusted hazard ratio (95% CI) of diabetes in individuals in the lowest quartile was 1.6 (1.3–2.0) in men and 1.7 (1.3–2.1) in women. These relationships were stronger in those who have never smoked.

CONCLUSIONS — Lower vital capacity is an independent predictor of incident type 2 diabetes. Pulmonary factors related to vital capacity deserve attention as possible risk factors for insulin resistance and diabetes.

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Impaired lung function has attracted growing interest as a potentially novel risk factor for glucose intolerance (1,2), insulin resistance (3), and type 2 diabetes (4,5,25). Possible mechanisms for the hypothesized link include direct effects of hypoxemia on glucose and insulin regulation (2,6), lung-related inflammatory mediators and their effects on insulin signaling (1,7,8), and adverse early-life exposures and their effects on organ development (9,10). Cross-sectional studies (11–14) have consistently shown that adults with diabetes have lower vital capacity than their nondiabetic counterparts, but such studies cannot establish temporal sequence. Prospective studies have tentatively identified lower vital capacity as a predictor of hyperinsulinemia (3) and type 2 diabetes (4,5,25) but have had limitations related to sample size and availability of diabetes-related data. We therefore analyzed longitudinal data from the Atherosclerosis Risk in Communities (ARIC) study, a biracial community-based study of 15,792 middle-aged adults, to test the hypothesis that lower lung function, as indicated by lower vital capacity, is cross-sectionally associated with features of insulin resistance and is an independent predictor of incident type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The ARIC study is an on-going, prospective cohort study designed to assess subclinical and clinical atherosclerosis in a cohort of adults aged 45–64 years, selected using probability sampling from the following four U.S. communities: Forsyth County, NC; Jackson, MS; the northwest suburbs of Minneapolis, MN; and Washington County, MD. By design, the Jackson site exclusively recruited African Americans, thereby accounting for 90% of African Americans in the study. Most of the remaining African Americans came from the Forsyth County cohort. The sampling procedure and methods used in the ARIC study have been previously described (15). The current study was based on 9-year follow-up data that included a baseline visit from 1987 through 1989 and three follow-up clinic visits scheduled 3 years apart. Of participants still alive at the time of the scheduled visits, response rates for the second, third, and fourth follow-ups were 93, 86, and 81%, respectively.

For the current analysis, individuals were excluded based on the following criteria: ethnicity other than black or white

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; DBP, diastolic blood pressure; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; SBP, systolic blood pressure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics of men and women according to FVC (% predicted) quartile*

	FVC (% predicted) quartile*				
	I (low) (< 90.8)	II (90.9–99.4)	III (99.5–108.4)	IV (high) (>108.4)	*P* for trend†
Men					
n	1,283	1,281	1,281	1,282	
African American	26	19	16	14	<0.0001
Age at baseline (years)	55 ± 5.6	54 ± 5.7	54 ± 5.6	53 ± 5.7	<0.0001
Education <12 years	26	20	20	15	<0.0001
Parental history of diabetes	12	13	12	10	0.11
Smoking status					
Current	36	27	22	18	<0.0001
Former	42	45	46	45	—
Never	22	28	32	37	—
Pack-years‡	36 ± 22.9	31 ± 23.8	28 ± 20.3	24 ± 18.4	<0.0001
Sport index	2.4 ± 0.8	2.6 ± 0.8	2.7 ± 0.8	2.8 ± 0.8	<0.0001
BMI (kg/m^2)	28.1 ± 4.6	27.5 ± 4.1	26.9 ± 3.6	26.6 ± 3.3	<0.0001
Waist-to-hip ratio	0.96 ± 0.06	0.96 ± 0.05	0.96 ± 0.05	0.94 ± 0.05	<0.0001
Height (cm)	176 ± 6.5	176 ± 6.5	176 ± 6.7	177 ± 6.6	0.06
Waist (cm)	101 ± 11.7	99 ± 10.4	97 ± 9.8	96 ± 9.1	<0.0001
Metabolic syndrome§	36	26	22	15	<0.0001
Fibrinogen (g/l)	3.1 ± 0.7	3.0 ± 0.6	2.9 ± 0.6	2.8 ± 0.6	<0.0001
White blood cell count (×10^9/l)	6.4 ± 1.9	6.2 ± 1.8	6.1 ± 2.6	5.9 ± 1.7	<0.0001
FVC (l)	3.8 ± 0.5	4.4 ± 0.5	4.8 ± 0.5	5.5 ± 0.6	<0.0001
FEV_1 (l)	2.7 ± 0.5	3.3 ± 0.5	3.6 ± 0.5	4.0 ± 0.6	<0.0001
FEV_1/FVC	72.9 ± 9.3	74.3 ± 7.4	74.2 ± 6.8	73.6 ± 6.4	0.05
	I (low) (< 95.7)	II (95.8–105.3)	III (105.4–114.6)	IV (high) (>114.6)	*P* for trend†
Women					
n	1,588	1,588	1,588	1,588	
African American	33	26	21	20	<0.0001
Age at baseline (years)	54 ± 5.8	53 ± 5.6	53 ± 5.6	54 ± 5.6	0.06
Education <12 years	26	19	17	15	<0.0001
Parental history of diabetes	12	13	14	13	0.71
Smoking status					
Current	34	22	19	15	<0.0001
Former	18	22	24	25	—
Never	48	56	57	60	—
Pack-years‡	25.0 ± 17.8	20.6 ± 17.3	17.6 ± 15.8	17.3 ± 15.6	<0.0001
Sport index	2.2 ± 0.7	2.3 ± 0.7	2.4 ± 0.8	2.5 ± 0.8	<0.0001
BMI (kg/m^2)	28.7 ± 6.6	27.3 ± 5.8	26.5 ± 5.1	26.1 ± 4.7	<0.0001
Waist-to-hip ratio	0.91 ± 0.08	0.89 ± 0.08	0.87 ± 0.08	0.87 ± 0.08	<0.0001
Height (cm)	163 ± 5.8	163 ± 5.9	162 ± 6.0	162 ± 6.1	<0.0001
Waist (cm)	98 ± 16.3	94 ± 14.9	91 ± 13.4	90 ± 12.8	<0.0001
Metabolic syndrome§	35	27	21	16	<0.0001
Fibrinogen (g/l)	3.2 ± 0.7	3.0 ± 0.6	2.9 ± 0.5	2.9 ± 0.6	<0.0001
WBC count (×10^9/l)	6.3 ± 1.9	5.9 ± 1.9	5.7 ± 1.6	5.5 ± 1.6	<0.0001
FVC (l)	2.7 ± 0.4	3.2 ± 0.4	3.5 ± 0.4	3.8 ± 0.5	<0.0001
FEV_1 (l)	2.0 ± 0.4	2.4 ± 0.3	2.6 ± 0.3	2.9 ± 0.4	<0.0001
FEV_1/FVC	76.0 ± 8.2	76.6 ± 6.1	76.2 ± 5.6	75.1 ± 5.8	0.46

Data are mean ± SD or percent. *Quartiles are sex specific. †*P* values correspond to tests for linear trend across quartiles. ‡Pack-years of cigarette smoking in ever-smokers only. §Metabolic syndrome was defined based on guidelines published in the National Cholesterol Education Program Adult Treatment Panel III report (46). The clinical identification of the metabolic syndrome is based upon the presence of any three of the following traits: *1*) abdominal obesity, defined as a waist circumference in men >102 cm (40 in) and in women >88 cm (35 in); *2*) serum triglycerides 150 mg/dl (1.7 mmol/l); *3*) serum HDL cholesterol <40 mg/dl (1 mmol/l) in men and <50 mg/dl (1.3 mmol/l) in women; *4*) blood pressure 130/85 mmHg; and *5*) fasting plasma glucose 110 mg/dl (6.1 mmol/l).

Table 2—*Adjusted levels of selected features of the insulin resistance syndrome by sex and FVC (% predicted) quartile at baseline: the ARIC study*

FVC quartile*	Fasting glucose (mg/dl)	Fasting insulin (μu/ml)	HOMA-IR†	HDL (mg/dl)	Triglycerides (mg/dl)	SBP (mmHg)	DBP (mmHg)
Men							
I (low)	101.5	12.5	3.2	43.5	148	122	75
II	100.2	11.1	2.8	44.6	137	121	75
III	100.5	10.6	2.7	44.3	134	121	75
IV (high)	100.1	10.0	2.5	46.1	124	119	74
P value‡	0.0004	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.12
Women							
I (low)	97.7	11.7	2.9	58.0	118	120	72
II	97.2	10.7	2.6	58.5	117	118	72
III	96.9	10.1	2.5	59.0	114	118	72
IV (high)	96.2	9.6	2.3	59.8	110	117	71
P value‡	<0.0001	<0.0001	< 0.0001	0.01	0.005	<0.0001	0.11

Adjusted simultaneously for age, race, waist circumference, pack-years of cigarette smoking, sport activity index, and ARIC center. HOMA-IR, homeostasis model assessment of insulin resistance. *Quartiles of FVC (% predicted) are sex specific. †HOMA-IR = (fasting insulin [μU/ml] × fasting glucose [mmol/l]/22.5). ‡*P* values correspond to tests for linear trend across quartiles.

(n = 48), preexisting diabetes at baseline (n = 1,867), missing data on spirometry or diabetes status at baseline (n = 192), no follow-up or with incomplete incident diabetes information (n = 873), missing data on relevant baseline covariates (n = 231), or self-reported asthma or chronic lung diseases (n = 1,102). The final study sample consisted of 11,479 adults without diabetes at baseline.

Spirometry

At the baseline visit, pulmonary function was assessed using a water-sealed Collin Survey II volume displacement spirometer (Warren E. Collins, Braintree, MA) with a computer interface. Calibration and analytic programs were installed on the computer to assist the operator in daily calibration, spirometric testing, and analysis. Measurement of forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were performed based on recommendations from the Epidemiology Standardization Project (16) and the American Thoracic Society (17). Participants were asked to perform a maximum of five forced expiratory maneuvers to obtain three acceptable spirograms, of which at least two were reproducible, defined as within ±5% of the FEV_1 and FVC. Acceptability and reproducibility were also indicated by the computer program and confirmed by the technician by observing the volume-time spirograms. Tests were performed by trained and certified pulmonary technicians. Methodology was standardized across the four field centers. Quality control and reproducibility were coordinated by a centralized pulmonary function reading center (Johns Hopkins School of Public Health, Baltimore, MD).

Incident type 2 diabetes

Individuals were classified as having diabetes if any of the following criteria, adapted from 1997 American Diabetes Association criteria, were met: fasting glucose level of at least 7.0 mmol/l (126 mg/dl) (90%), nonfasting glucose level of at least 11.1 mmol/l (200 mg/l) (1%), current use of antidiabetic medication (1%), or a positive response to the question "Has a doctor ever told you that you had diabetes (sugar in the blood)?" (8%). Persons classified as having diabetes at baseline were excluded.

Other baseline variables

The definitions and methods used for other baseline measurements (age, race, education level, cigarette smoking status and pack-years, sport activity index, blood pressure, parental history of diabetes, height, BMI, waist and hip circumferences, HDL cholesterol, triglycerides, glucose, insulin, white blood cell count, and fibrinogen) have been previously reported (7,18). C-reactive protein was assessed in a subgroup of 581 incident cases of type 2 diabetes and a comparison cohort of 572 noncases (19). Birth weight was self-reported at the fourth scheduled follow-up. If participants did not know their birth weights, they were asked to report birth weight categories: low (<5 1/2 lb), medium (5 1/2 to 9 lb), or high (>9 lb).

Data analysis

Predicted FVC and FEV_1 were calculated by the ARIC Data Coordinating Center using the equations developed by Crapo, Morris, and Gardner (20) in nonsmokers that included age, sex, height, and race. Before analysis, crude data on FVC and FEV_1 were divided by predicted FVC and FEV_1, respectively, to yield FVC (% predicted) and FEV_1 (% predicted). Because lung capacity differs dramatically in men and women, all analyses were stratified by sex. Distributions of FVC (% predicted) and FEV_1 (% predicted) were approximately normal and were categorized into sex-specific quartiles. Highest quartiles were used as reference groups. Means and frequencies of potential confounders assessed at the baseline visit were determined for each quartile of FVC (% predicted) and FEV_1 (% predicted). ANOVA and χ^2 analysis were used to assess the statistical significance of the differences across quartiles.

To determine associations between vital capacity and features of the insulin resistance syndrome, a series of cross-sectional analyses were performed using data at baseline among nondiabetic participants. The relation between quartiles of FVC (% predicted) and FEV_1 (% pre-

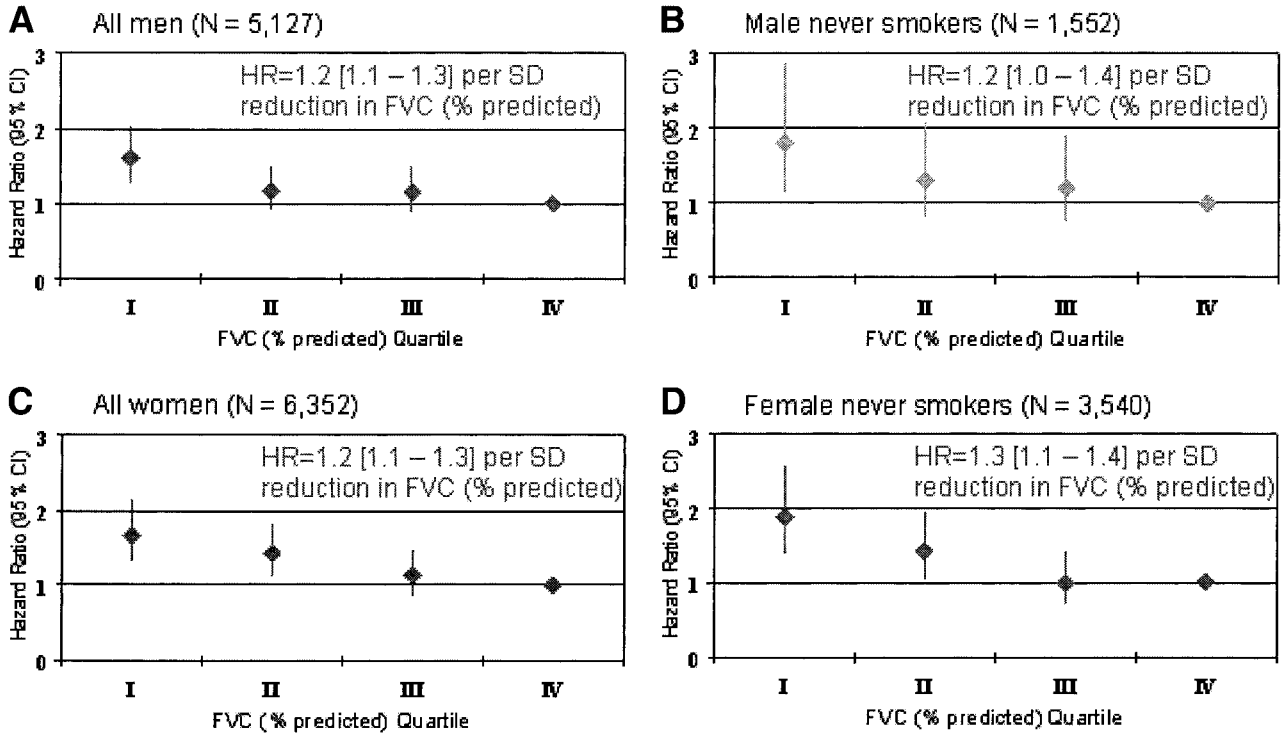

Figure 1—*Nine-year adjusted hazard ratios (HR) for incident diabetes by FVC (% predicted) quartile, sex, and smoking status. All hazard ratios are simultaneously adjusted for age, race, pack-years of cigarette smoking (A and C), waist circumference, sport activity index, and ARIC center. FVC (% predicted) quartiles are categorized based on sex-specific values in total population. I indicates the lowest FVC quartile and IV the highest. Bars indicate 95% CIs.*

dicted) and fasting insulin, fasting glucose, total triglycerides, HDL cholesterol, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were assessed by using linear regression models, after adjustment for confounding factors including age, race, pack-years of smoking, waist circumference, sport activity index (scale one [lowest] to five [highest]), and ARIC center.

Incidence rates of diabetes were calculated for each quartile of FVC (% predicted) and FEV_1 (% predicted) using a person-years approach. For participants without diabetes, person-years were calculated from baseline to the last visit date. Incident cases were assumed to have occurred at the midpoint between the last visit at which diabetes was found to be absent and the first visit at which diabetes was found to be present.

Time to incident diabetes was assessed by quartiles of FVC (% predicted) and FEV_1 (% predicted) using survival analysis. Cox proportional hazards models were used for the multivariable analysis when the data met the proportionality assumption implicit in the models. Relative hazard ratios were used to compare the risk of incident diabetes in lower three versus the highest quartile of FVC (% predicted) and FEV_1 (% predicted) after adjustment for confounding factors. To minimize the possibility of residual confounding secondary to smoking, multivariable analyses were repeated in never-smokers. Additional multivariable analyses were performed to investigate the roles of inflammatory markers and low birth weight as potential confounders. All tests of significance were two-tailed, with an α level of 0.05. All analyses were performed using SAS (Cary, NC) statistical software package (version 8.01).

RESULTS

Baseline characteristics and cross-sectional associations

Baseline characteristics for men and women are shown in Table 1 by quartiles of FVC (% predicted). In both groups, individuals with lower FVC (% predicted) were significantly more likely to be African American, older, and less educated; to have smoked more cigarettes; to be less physically active; to have higher BMI, waist circumference, and waist-to-hip ratio; were more likely to have metabolic syndrome; and to have higher blood levels of white cell counts and fibrinogen. As expected, adults with low FVC (% predicted) also tended to have low FVC and FEV_1.

To determine whether a lower vital capacity was associated at baseline with features of the insulin resistance syndrome, cross-sectional analyses were performed (Table 2). In men and women, lower FVC (% predicted) was independently associated with higher fasting glucose, insulin, and triglycerides; higher SBP; and lower HDL cholesterol. There was no association between FVC (% predicted) and DBP.

Incident type 2 diabetes

During 9 years of follow-up, 673 men and 673 women developed type 2 diabetes. In both groups, there were graded inverse relationships between FVC (% predicted) and incidence rates of type 2 diabetes. In men, diabetes incidence rose from 11.3 per 1,000 person-years in the highest FVC (% predicted) quartile to 28.3 per 1,000 person-years in the lowest FVC (%

predicted) quartile, corresponding to an age- and race-adjusted relative risk of 2.4 (95% CI 1.9–3.0). In women, diabetes incidence rose from 7.9 per 1,000 person-years in the highest FVC (% predicted) quartile to 22.9 per 1,000 person-years in the lowest FVC (% predicted) quartile, corresponding to an age- and race-adjusted relative risk of 2.5 (2.0–3.2).

Multivariable analyses of FVC (% predicted)

In multivariable analyses using the Cox proportional hazards models, the significant graded inverse association between FVC (% predicted) and incidence of diabetes persisted in both men and women after adjustment for age, race, pack-years of smoking, waist circumference, sport activity index, and ARIC center (Figs. 1*A* and *C*). Compared with individuals in the highest quartile of FVC (% predicted), the adjusted hazard ratio (95% CI) of diabetes in individuals in the lowest quartile was 1.6 (1.3–2.0) in men and 1.7 (1.3–2.1) in women. Additional adjustment for presence of the metabolic syndrome attenuated the association slightly: compared with their counterparts in the highest quartile of FVC (% predicted), men and women in the lowest quartile of FVC (% predicted) remained 1.4-fold (95% CI 1.1–1.8) and 1.5-fold (1.2–1.9) more likely to develop type 2 diabetes, respectively. Adjustment for fasting glucose, homeostasis model assessment of insulin resistance, and SBP rather than metabolic syndrome produced a similar attenuation: compared with their counterparts in the highest quartile of FVC (% predicted), men and women in the lowest quartile of FVC (% predicted) were 1.3-fold (1.0–1.7) and 1.4-fold (1.1–1.8) more likely to develop type 2 diabetes, respectively.

To minimize the possibility of residual confounding due to cigarette smoking, analyses were repeated after restricting the sample to adults who never smoked (Figs. 1*B* and *D*). In both men and women who never smoked, the associations were stronger than in the full population: men and women in the lowest quartile of FVC (% predicted) had 1.9-fold (95% CI 1.2–3.0) and 1.9-fold (1.4–2.6) risk of developing type 2 diabetes, respectively, compared with the individuals in the highest quartiles of FVC (% predicted).

Subsidiary analyses

To investigate the relationship of FVC (% predicted) to other emerging predictors of diabetes risk, we conducted subsidiary analyses in the full cohort (smokers and nonsmokers). First, to determine whether FVC-related differences in inflammatory markers might help explain the relationship of lower FVC (% predicted) to diabetes risk, we performed additional analyses after introducing white cell count and plasma fibrinogen concentration into multivariable models that already included age, race, waist circumference, smoking, sport activity index, and ARIC center. In a case-cohort subgroup of 1,153 participants, we additionally adjusted for C-reactive protein. In neither analysis did adjustment for inflammatory markers influence associations between lower FVC and incident type 2 diabetes. For example, in men in the case-cohort subgroup, the fully adjusted hazard ratios (95% CI) of incident diabetes in the third, second, and first (lowest) quartile of FVC (% predicted) compared with those in the fourth (highest) quartile were 1.3 (0.7–2.7), 1.4 (0.6–2.8), and 2.1 (1.1–3.9), respectively (*P* for trend = 0.04, data not shown).

Second, in a subset of individuals for whom data on birth weight or birth weight categories were available (~80%), we conducted analyses to determine *A*) the relationship of low birth weight with low FVC (% predicted) and *B*) the extent to which the FVC (% predicted)–diabetes association was explained by low birth weight. In multivariable analyses that adjusted for age and race, FVC (% predicted) was positively correlated with birth weight in men (β coefficient = 0.5% per lb, $P = 0.007$) but not in women (β coefficient = −0.1% per lb, $P = 0.47$). The relationship of FVC (% predicted) to incident diabetes was largely independent of low birth weight. In multivariable analyses that included both FVC (% predicted) and low birth weight, as well as age, race, waist circumference, pack-years of smoking, sport index, and ARIC center, low FVC (% predicted) remained significantly associated with diabetes risk in a graded fashion: in these models, men and women in the lowest quartiles of FVC (% predicted) remained 1.7-fold (95% CI 1.3–2.1) and 1.7-fold (1.3–2.2) more likely to develop type 2 diabetes, respectively, than their counterparts in the highest quartiles of FVC (% predicted).

FEV_1 (% predicted) and incident type 2 diabetes

When FEV_1 (% predicted) was used as an indicator of lung function, similar patterns of results were obtained. For example, in multivariable models adjusting for age, race, waist circumference, pack-years of smoking, sport index, and ARIC center, compared with their counterparts in the highest quartile of FEV_1 (% predicted), men in the lowest quartile were 1.7-fold (95%CI 1.3–2.1) as likely to develop type 2 diabetes, and women in the lowest quartile were 1.5-fold (1.1–1.9) as likely. In contrast, there was no association between the ratio of FEV_1 to FVC and the subsequent risk of incident diabetes in either men or women (data not shown).

CONCLUSIONS — In this prospective study of middle-aged men and women without known lung disease, lower vital capacity predicted the subsequent development of type 2 diabetes. The association was graded, was independent of a variety of potentially confounding factors, was stronger in never smokers, and was similar in magnitude to well-established diabetes risk factors like physical inactivity and family history of diabetes (21,22). It also appeared to be specific to vital capacity, since the ratio of FEV_1 to FVC, an indicator of obstructive airways disease, was not at all related to diabetes risk. Moreover, adults with lower FVC (% predicted) had many features of insulin resistance at baseline, including higher blood levels of glucose, insulin, and triglycerides; lower HDL cholesterol; and higher SBP.

Our results are generally consistent with previous prospective studies on lung function and the subsequent occurrence of diabetes and related conditions. In 1,050 initially nondiabetic healthy male veterans in the Normative Aging Study, Lazarus, Sparrow, and Weiss (3) found that lower FVC, lower FEV_1, and lower maximal midexpiratory flow rate at baseline predicted hyperinsulinemia and estimated insulin resistance over 20 years of follow-up, independent of age, adiposity, and smoking. In a Swedish study (23) of 4,637 nondiabetic middle-aged men, baseline mean vital capacity was 10% lower among 116 men who developed diabetes during 6-years follow-up than those who did not develop diabetes. More recently, Engstrom et al. (4) reported on 382 initially nondiabetic Swedish men

born in 1914 who underwent spirometry at age 55 years. In this cohort, low FVC and FEV_1 predicted the presence of diabetes at follow-up 13 years later, independent of adiposity and weight gain. However, the use of urine test strips to screen for diabetes at baseline raises concern about the possible inclusion of adults with preexisting diabetes into the inception cohort. Later on, Engstrom et al. (5) confirmed this finding in a larger cohort of Swedish men and women. This study also found incidence of cardiovascular diseases was significantly increased among subjects with low FVC (% predicted) who had developed insulin resistance. This observation suggested insulin resistance may be a mediator between low FVC (% predicted) and cardiovascular disease, which has been noted previously (24). Finally, Ford and Mannino (25) reported that FVC and FEV_1 but not the ratio of FEV_1 to FVC were significantly and inversely associated with the incidence of diabetes in the National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study. That study also found that restrictive lung disease was significantly associated with the incidence of diabetes but not obstructive lung disease. Nevertheless, the above studies were limited to whites (4,5,23), used nonstandard spirometry methods (5,25), or had a relatively small number of incident cases, which precluded extensive simultaneous adjustment for potential confounders (4,5,23).

One possible explanation for the link between low vital capacity and diabetes risk is related to hypoxemia-induced insulin resistance. Experimental hypoxia produces insulin resistance and hyperinsulinemia in animals (26,27). In humans, lower vital capacity can be associated with lower oxygen saturation at rest with further worsening with exertion (28). Moreover, exposure to altitude hypoxia (2) or hypobaric hypoxia (6) can reduce insulin sensitivity and predispose to the development of type 2 diabetes. These effects may be partially mediated by sympathetic nerve activity: hypoxia increases sympathetic nerve activity (29,30), and in the ARIC study, indicators of sympathetic nerve activity (low heart rate variability and high heart rate) independently predict incident diabetes (31). However, the mild decrements lung function, as noted in the current analyses, are not likely to be associated with significant hypoxemia, thus making it a less plausible intermediate in the putative causal pathway linking low FVC with incident type 2 diabetes. Moreover, several lines of conflicting evidence suggest that hypoxemia may have no harmful effects in insulin sensitivity (32–36).

Another possible explanation is that lower vital capacity and risk of diabetes are both partially determined by adverse fetal or early-life conditions via effects on organogenesis and metabolic pathway programming, which, through long-standing altered gene expression, would favor resistance to insulin action. Prior studies suggest that low birth weight is associated in adults with reduced lung function (10), reduced β-cell function (37), insulin resistance (38), and an increased incidence of type 2 diabetes (39). Moreover, in adults, shorter leg length, an indicator of adverse environmental influences on prepubertal development, is associated with lower FVC and FEV_1 (40) and with impaired glucose tolerance (41). Under this hypothesis, lower vital capacity might either represent a marker of underdevelopment without a direct role in diabetes pathophysiology or might be a mediator of the adverse metabolic effects of underdevelopment. Indeed, we found that low FVC (% predicted) was associated with low birth weight. However, the relation of FVC (% predicted) to incident diabetes was largely independent of low birth weight, which suggests a distinct pathway from low FVC to diabetes risk.

A third possible explanation involves some relationship of low vital capacity to emerging inflammatory precursors of insulin resistance and diabetes (7). Nuclear factor interleukin-6, early growth response-1, and hypoxia-inducible factor-1 mediate inflammatory responses to chronic hypoxia in macrophages, pulmonary vascular endothelium, and smooth muscle (8). Cigarette smoking, recently established as an independent predictor of type 2 diabetes (42,43), provokes an inflammatory response (44) and is inversely associated with vital capacity. However, in our study, the link between lower vital capacity and diabetes risk was completely independent of cigarette exposure and was stronger in never-smokers. Furthermore, reduced vital capacity is a common residual effect of lower respiratory tract infections, including those in childhood and infancy (10), that might provoke an inflammatory response. In any case, our subsidiary analyses of white cell count or plasma fibrinogen suggested little or no explanatory role for these two general markers of inflammation, although we lacked sufficient data on other more specific markers to exclude a role for inflammation conclusively.

Finally, decreased muscle strength might be the link between impaired lung function and hyperinsulinemia (3). Ventilatory function is partially determined by respiratory muscle strength; low level of skeletal muscle strength (as indicated by hand-grip strength) predicted higher levels of fasting insulin in the Normative Aging Study (45). However, no data on muscle strength were available in the ARIC study to test this hypothesis.

Strengths of this study include a community-based sampling method, standardized spirometric techniques, extensive data on potential confounders, and a large sample size that increased precision and permitted multiple statistical adjustments. The study's main limitation was lack of data on insulin sensitivity, oxygen saturation, visceral fat, and specific inflammatory markers, which precluded more detailed investigation of causal pathways. Self-reported birth weight data may also be subject to recall bias and misclassification. Finally, we could not establish temporal sequence for the cross-sectional relationship between insulin resistance and reduced lung function that we observed at baseline.

The main implication of our study is that lower vital capacity of the lung deserves attention as an emerging, novel risk factor for type 2 diabetes. Even if it turns out not to lie within a causal pathway to diabetes, FVC might still be a useful risk predictor, and the FVC-diabetes link could suggest explanations for other phenomena, like the elevated risk of heart disease associated with low vital capacity. On the other hand, if vital capacity does indeed lie in a casual pathway, then pathophysiologic derangements associated with lower FVC, like hypoxemia and lung-related inflammation, might represent novel targets for interventions aimed at the primary prevention of type 2 diabetes.

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References

1. Hjalmarsen A, Aasebo U, Birkeland K, Sager G, Jorde R: Impaired glucose tolerance in patients with chronic hypoxic pulmonary disease. *Diabetes Metab* 22:37–42, 1996
2. Larsen JJ, Hansen JM, Olsen NV, Galbo H, Dela F: The effect of altitude hypoxia on glucose homeostasis in men. *J Physiol* 504: 241–249, 1997
3. Lazarus R, Sparrow D, Weiss ST: Baseline ventilatory function predicts the development of higher levels of fasting insulin and fasting insulin resistance index: the Normative Aging Study. *Eur Respir J* 12:641–645, 1998
4. Engstrom G, Janzon L: Risk of developing diabetes is inversely related to lung function: a population-based cohort study. *Diabet Med* 19:167–170, 2002
5. Engstrom G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L: Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study. *J Intern Med* 253:574–581, 2003
6. Braun B, Rock PB, Zamudio S, Wolfel GE, Mazzeo RS, Muza SR, Fulco CS, Moore LG, Butterfield GE: Women at altitude: short-term exposure to hypoxia and/or alpha(1)-adrenergic blockade reduces insulin sensitivity. *J Appl Physiol* 91:623–631, 2001
7. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, Offenbacher S, Azambuja MI, Tracy RP, Heiss G: Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. *Lancet* 353:1649–1652, 1999
8. Semenza GL: Oxygen-regulated transcription factors and their role in pulmonary disease. *Respir Res* 1:159–162, 2000
9. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD: Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 303:1019–1022, 1991
10. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO: Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 303:671–675, 1991
11. Lange P, Groth S, Kastrup J, Mortensen J, Appleyard M, Nyboe J, Jensen G, Schnohr P: Diabetes mellitus, plasma glucose and lung function in a cross-sectional population study. *Eur Rrespir J* 2:14–19, 1989
12. Barrett-Connor E, Frette C: NIDDM, impaired glucose tolerance, and pulmonary function in older adults: the Rancho Bernardo Study. *Diabetes Care* 19:1441–1444, 1996
13. Davis TME, Knuiman M, Kendall P, Vu H, Davis WA: Reduced pulmonary function and its association in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Res Clin Pract* 50:153–159, 2000
14. Walter RE, Beiser A, Givelber RJ, O'Connor GT, Gottlieb DJ: Association between glycemic state and lung function: the Framingham Heart Study. *Am J Respir Crit Care Med* 167:911–916, 2003
15. The ARIC Investigators: The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol* 129: 687–702, 1989
16. Ferris BG Jr, Speizer FE, Bishop Y, Prang G, Weener J: Spirometry for an epidemiologic study: Deriving optimum summary statistics for each subject. *Bull Europ Physiopath Resp* 14:146–166, 1978
17. Gardner RM, et al.: ATS statement: Snowbird workshop on standarization of spirometry. *Am Rev Respir Dis* 119:831–838, 1979
18. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M: Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. *JAMA* 283:2253–2259, 2000
19. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, Hoogeveen R, Folsom AR, Heiss G, the Atherosclerosis Risk in Communities Study: Low-grade systemic inflammation and the development of type 2 diabetes: the Atherosclerosis Risk in Communities Study. *Diabetes* 52:1799–1805, 2003
20. Crapo RO, Morris AH, Gardner RM: Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 123: 659–664, 1981
21. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE: Physical activity and incidence of non-insulin dependent diabetes mellitus in women. *Lancet* 338:774–778, 1991
22. Shaten BJ, Smith GD, Kuller LH, and Neaton JD: Risk factors for the development of type II diabetes among men enrolled in the usual care group of the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:1331–1339, 1993
23. Eriksson KF, Lindgarde F: Poor physical fitness, and impaired early insulin response but late hyperinsulinaemia, as predictors of NIDDM in middle-aged Swedish men. *Diabetologia* 39:573–579, 1996
24. Kannel WB, Hubert H, Lew EA: Vital capacity as a predictor of cardiovascular disease: the Framingham study. *Am Heart J* 105:311–315, 1983
25. Ford ES, Mannino DM: 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* 27:2966–2970, 2004
26. Cheng N, Cai W, Jiang M, Wu S: Effect of hypoxia on blood glucose, hormones, and insulin receptor functions in newborn calves. *Pediatr Res* 41:852–856, 1997
27. Raff H, Bruder ED, Jankowski BM: The effect of hypoxia on plasma leptin and insulin in newborn and juvenile rats. *Endocrine* 11:37–39, 1999
28. Pollard AJ, Barry PW, Mason NP, Collier DJ, Pollard RC, Pollard PF, Martin I, Fraser RS, Miller MR, Milledge JS: Hypoxia, hypocapnia and spirometry at altitude. *Clin Sci (Lond)* 92:593–598, 1997
29. Halliwill JR, Minson CT: Effect of hypoxia on arterial baroreflex control of heart rate and muscle sympathetic nerve activity in humans. *J Appl Physiol* 93:857–864, 2002
30. Smith ML, Muenter NK: Effects of hypoxia on sympathetic neural control in humans. *Respir Physiol* 121:163–171, 2000
31. Carnethon MR, Golden SH, Folsom AR, Haskell W, Liao D: A prospective investigation of autonomic nervous system function and the development of type 2 diabetes: the Atherosclerosis Risk in Communities Study, 1987–1998. *Circulation* 107:2190–2195, 2003
32. Santos JL, Perez-Bravo F, Carrasco E, Calvillan M, Albala C: Low prevalence of type 2 diabetes despite a high average body mass index in the Aymara natives from Chile. *Nutrition* 17:305–309, 2001
33. de Glisezinski I, Crampes F, Harant I, Havlik P, Gardette B, Jammes Y, Souberbielle JC, Richalet JP, Riviere D: Decrease of subcutaneous adipose tissue lipolysis after exposure to hypoxia during a simulated ascent of Mt Everest. *Pflugers Arch* 439:134–140, 1999
34. Lee WC, Chen JJ, Hunt DD, Hou CW, Lai YC, Lin FC, Chen CY, Lin CH, Liao YH, Kuo CH: Effects of hiking at altitude on body composition and insulin sensitivity in recovering drug addicts. *Prev Med* 39: 681–688, 2004
35. Sauerwein HP, Schols AM: Glucose metabolism in chronic lung disease. *Clin Nutr* 21:367–371, 2002
36. Krampl E, Kametas NA, Nowotny P, Roden M, Nicolaides KH: Glucose metabolism in pregnancy at high altitude. *Diabetes Care* 24:817–822, 2001
37. Cook JT, Levy JC, Page RC, Shaw JA, Hattersley AT, Turner RC: Association of low

birth weight with beta cell function in the adult first degree relatives of non-insulin dependent diabetic subjects. *BMJ* 306: 302–306, 1993
38. Phillips DI, Barker DJ, Hales CN, Hirst S, Osmond C: Thinness at birth and insulin resistance in adult life. *Diabetologia* 37: 150–154, 1994
39. Forsen T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C, Barker D: The fetal and childhood growth of persons who develop type 2 diabetes. *Ann Intern Med* 133: 176–182, 2000
40. Gunnell D, Whitley E, Upton MN, McConnachie A, Davey Smith G, Watt GC: Associations of height, leg length, and lung function with cardiovascular risk factors in the Midspan Family Study. *J Epidemiol Community Health* 57:141–146, 2003
41. Asao K, Kao WHL, Baptiste-Roberts K, Bandeen-Roche K, Erlinger T, Brancati L: Upper leg length and glucose tolerance in U.S. adults: NHANES III (Abstract). *Circulation* 107:E7005, 2003
42. Wannamethee SG, Shaper AG, Perry IJ, the British Regional Heart Study: Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. *Diabetes Care* 24:1590–1595, 2001
43. Manson JE, Ajani UA, Liu S, Nathan DM, Hennekens CH: A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. *Am J Med* 109:538–542, 2000
44. Zalokar JB, Richard JL, Claude JR: Leukocyte count, smoking, and myocardial infarction. *N Engl J Med* 304:465–468, 1981
45. Lazarus R, Sparrow D, Weiss ST: Handgrip strength and insulin levels: cross-sectional and prospective associations in the Normative Aging Study. *Metabolism* 46: 1266–1269, 1997
46. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001