Low Lung Function and Risk of Type 2 Diabetes in Japanese Men: The Toranomon Hospital Health Management Center Study 9 (TOPICS 9)

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Abstract

Objective: To evaluate the effect of elevated fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c}) concentrations on lung dysfunction and to prospectively investigate whether reduced lung function would be independently predictive of diabetes.

Participants and Methods: From January 6, 1997, through December 22, 2008, we observed 5346 men with no history of diabetes or lung dysfunction. Hazard ratios (HRs) for incident diabetes (FPG ≥ 126 mg/dL, HbA_{1c} $\geq 6.5\%$, or self-reported clinician-diagnosed diabetes) were estimated for spirometry indices as continuous and categorical variables.

Results: Elevated HbA_{1c} concentrations within the normal range were significantly and more strongly associated with reduced forced vital capacity and forced expiratory volume in the first second after expiration (FEV₁) than were FPG concentrations. During a 4.0-year follow-up, diabetes developed in 214 individuals. A 10-point decrease in percentage of FEV₁ predicted value was associated with an increased HR of 1.21 (95% confidence interval [CI], 1.09-1.34; $P = .001$) for diabetes after adjustment for demographic factors and body mass index. This association remained significant even after adjustment for metabolic factors, smoking status, and FPG or HbA_{1c} concentrations but was attenuated substantially after adjustment for baseline HbA_{1c} values (HR, 1.13; 95% CI, 1.01-1.26; $P = .03$). Lower quartile (Q) categories of percentage of FEV₁ predicted value were associated with increased risk of diabetes independently of known predictors including HbA_{1c} (HR, 1.73; 95% CI, 1.14-2.62 for Q1; and HR, 1.76; 95% CI, 1.15-2.69 for Q2).

Conclusion: Reduced lung function was significantly related to chronic glycemic exposure within a normal range. Relatively low pulmonary function was an independent risk factor for diabetes in apparently healthy Japanese men.

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Evidence has suggested that individuals with diabetes have impaired lung function.^{1,2} However, an inverse association between lung function and the prediabetic state, including impaired fasting plasma glucose (FPG) and elevated hemoglobin A_{1c} (HbA_{1c}) concentrations, has not yet been clarified in individuals without diabetes. Although studies have reported that impairment of lung function preceded the development of diabetes,³⁻¹⁰ results of investigations of the association of lung dysfunction and hyperglycemia in individuals without diabetes have been inconsistent.^{4,11-14} Inasmuch as a bidirectional association in which chronic hyperglycemia might reduce pulmonary function has been suggested in patients with diabetes,^{15,16} it should be elucidated whether low pulmonary function is predictive of development of diabetes independently of glycemic exposure including elevated FPG or HbA_{1c} concentrations. Therefore, in the

present cross-sectional study, we investigated the effect of elevated FPG and HbA_{1c} concentrations on lung function and prospectively assessed whether impaired lung function would be an independent predictor of the development of diabetes in a cohort consisting of apparently healthy Japanese men.

PARTICIPANTS AND METHODS

Study Population

The Toranomon Hospital Health Management Center Study included a cohort consisting primarily of apparently healthy government employees who underwent annual health examinations for health screening in Tokyo, Japan. At each annual physical examination, anthropometric measurements were obtained, biochemical tests were performed, and participants were interviewed using standard ques-

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tionnaires that gathered information on demographic characteristics, medical history, and health-related habits. Routine health checkups are common in Japan because the Japanese government and private companies encourage people to undergo periodic examinations.¹⁷ For the present analysis involving 24,814 men and 9844 women who underwent annual medical examinations, with baseline examinations performed from January 6, 1997 to December 27, 2004, we examined data for 5810 men who underwent repeated examinations at 2 and 4 years after the baseline examination, that is, from January 6, 1997, through December 22, 2008. Women were not included as study subjects because the database did not contain a sufficient number of incident cases of diabetes in women for a meaningful analysis (20 incident cases per 1842 women after exclusions). Of the 5810 men, we excluded 305 who had diabetes at the baseline examination (previously diagnosed in 173 and detected at the baseline examination in 132), 96 who had a self-reported history of asthma or other chronic lung dysfunction, and 72 with missing data on baseline characteristics. Of the 5810 men, 9 had both diabetes and lung dysfunction at baseline examination or had missing data, and were, therefore, counted twice; thus, overall, 464 individuals were excluded from the 5810 originally considered as study participants. Subsequently, 5346 men aged 22 to 80 years were eligible for analysis. Diagnosis of baseline and incident diabetes was defined according to American Diabetes Association criteria of FPG concentration of 126 mg/dL or more (to convert to mmol/L, multiply by 0.05551), self-reported clinician-diagnosed diabetes, or HbA_{1c} concentration of 6.5% or higher.¹⁸

Spirometry

Spirometry was performed, and forced vital capacity (FVC) and forced expiratory volume in the first second of expiration (FEV₁) were measured by trained staff. Spirometric measurements of FVC and FEV₁, percentage of FVC for predicted values (FVC_{%pre}), and percentage of FEV₁ for predicted values (FEV_{1%}pre) were used as markers of restrictive lung dysfunction. The FEV₁:FVC ratio was calculated by dividing the measured FEV₁ by the measured FVC as a marker of obstructive lung dysfunction.^{19,20} The predicted FVC and predicted FEV₁ were calculated by height and age using the equations for men. Percentage of predicted FVC and FEV_{1%}pre were calculated using the following equations recommended by the Japanese Respiratory Society²¹: FVC_{%pre} = FVC/predicted FVC (0.042 × height – 0.024 × age – 1.785) and FEV_{1%}pre = FEV₁/predicted FEV₁ (0.036 × height – 0.028 × age – 1.178).

Other Variables

Blood samples were collected after an overnight fast (12 hours) and measured using an automatic clinical chemistry analyzer (LABOSPECT 008, Hitachi, Ltd, Tokyo, Japan). Blood glucose, serum triglyceride, and high-density lipoprotein cholesterol concentrations were measured using enzymatic methods. Hemoglobin A_{1c} was assessed using high-performance liquid chromatography. The value for HbA_{1c} (%) was estimated as the National Glycohemoglobin Standardization Program equivalent value (%) calculated using the formula HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society) (%) + 0.4%.²²

Statistical Analyses

In the cross-sectional analysis, multiple linear regression models were performed to assess the association of FPG and HbA_{1c} concentrations with FVC and FEV using data obtained at the baseline examination. We also calculated odds ratios (ORs) to evaluate the probability of impaired fasting glucose concentration (FPG 100-125 mg/dL) or elevated HbA_{1c} value (HbA_{1c} 5.7%-6.4%)¹⁸ according to quartile categories of spirometry indices. In the prospective analysis, duration of follow-up for each participant was calculated from the date of the first examination to the date of confirmed diabetes or the date of the last follow-up examination. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) for incident diabetes that included spirometry indices as continuous and categorical variables. Tests for a linear trend across increasing categories of spirometry indices were conducted by treating the categories as continuous variables in a model. Statistical analyses were performed using IBM SPSS Statistics version 19 (IBM Corp, Armonk, NY), and statistical significance was considered at *P* < .05. The study protocol was consistent with the Japanese government's Ethical Guidelines Regarding Epidemiological Studies in accordance with the Declaration of Helsinki and was reviewed by the Institutional Review Board of Toranomon Hospital.

RESULTS

Association of Elevated HbA_{1c} and FPG Concentrations With Lung Dysfunction at Baseline Examination

Baseline characteristics of the total study population and those in whom diabetes did or did not develop are given in Table 1. During a 4-year follow-up, type 2 diabetes developed in 214 individuals. From the unadjusted results given in Table 1, we observed that individuals in whom diabetes developed had significantly higher FPG and HbA_{1c} values and lower FVC, FEV₁, FVC_{%pre}, and

TABLE 1. Baseline Characteristics of the Entire Study Population and Individuals Who Did or Did Not Develop Diabetes During Follow-up^{a-c}

Variable	Total No. of Patients (N=5346)	Incidence of diabetes		P value ^d
		No diabetes (n=5132)	Diabetes (n=214)	
Age (y)	48.6 (8.9)	48.5 (8.9)	51.6 (8.4)	<.001
FVC (L)	4.32 (0.65)	4.33 (0.65)	4.05 (0.66)	<.001
FEV ₁ (L)	3.42 (0.57)	3.43 (0.56)	3.19 (0.56)	<.001
FVC _{%pre} (%)	103.9 (12.1)	104.1 (12.1)	100.4 (11.9)	<.001
FEV _{1%} pre (%)	96.3 (11.8)	96.4 (11.8)	93.0 (11.5)	<.001
FEV ₁ :FVC ratio (%)	79.3 (6.4)	79.3 (6.5)	78.7 (5.6)	.22
Parental history of diabetes	731 (13.7)	678 (13.2)	53 (24.8)	<.001
Physical activity, yes	2686 (50.2)	2583 (50.3)	103 (48.1)	.53
Smoking status				.02
Never	2254 (42.2)	2184 (42.6)	70 (32.7)	
Former	1576 (29.5)	1502 (29.3)	74 (34.6)	
Current	1516 (28.4)	1446 (28.2)	70 (32.7)	
Body mass index	23.3 (2.7)	23.3 (2.7)	24.2 (3.2)	<.001
Blood pressure (mm Hg)				
Systolic	127 (15)	126 (15)	132 (18)	<.001
Diastolic	78 (11)	78 (11)	81 (12)	<.001
Hypertension ^e	1217 (22.8)	1142 (22.3)	75 (35.0)	<.001
Triglycerides (mg/dL)	126.0 (81.1)	125.0 (80.3)	151.8 (94.9)	<.001
Total cholesterol (mg/dL)	201.5 (31.6)	201.5 (31.6)	202.3 (31.6)	.71
HDL cholesterol (mg/dL)	51.0 (13.6)	51.2 (13.6)	47.3 (13.8)	<.001
Fasting plasma glucose (mg/dL)	96.2 (8.3)	95.6 (7.8)	109.5 (9.3)	<.001
HbA _{1c} (%)	5.3 (0.3)	5.3 (0.3)	5.8 (0.4)	<.001

^aFEV₁ = forced expiratory volume in the first second of expiration; FEV_{1%}pre = FEV₁ for predicted values; FVC = forced vital capacity; FVC_{%pre} = FVC for predicted values; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein.

^bData are presented as mean (SD) or number (%) unless otherwise indicated.

^cSI conversion factors: To convert triglyceride values to mmol/L, multiply by 0.01129; to convert total cholesterol and HDL cholesterol values to mmol/L, multiply by 0.02586; to convert fasting plasma glucose concentrations to mmol/L, multiply by 0.05551.

^dP values were tested using the *t* test for continuous variables, and categorical data were analyzed using the χ^2 test.

^eHypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg or treatment.

FEV_{1%}pre than did those in whom diabetes did not develop. The FEV₁:FVC ratio was also lower in the individuals with diabetes, but without statistical significance ($P=.22$).

When we investigated a possible association of FPG and HbA_{1c} values with lung function at the baseline examination, with adjustments for age, body mass index, current smoking status, and physical activity status, we observed that FPG concentrations were not significantly and inversely associated with lung function. In contrast, the association of lung function indices with HbA_{1c} values was significant (Supplemental Table 1, available online at <http://www.mayoclinicproceedings.org>). Compared with individuals with FPG values less than 100 mg/dL, those with FPG values of 100 to 109 mg/dL had FVC of -1.5 mL (95% confidence interval [CI], -39.4 to 36.5 ; $P=.94$) and FEV₁ of 10.3 mL (95% CI, -19.9

to 40.4 ; $P=.50$), and those with FPG concentrations of 110 to 125 mg/dL had FVC of -32.0 mL (95% CI, -95.4 to 31.3 ; $P=.32$) and FEV₁ of 4.5 mL (95% CI, -45.9 to 54.9 ; $P=.86$). Compared with individuals with HbA_{1c} values less than 5.7%, those with HbA_{1c} values of 5.7% to 5.9% had FVC of -65.2 mL (95% CI, -118.6 to -11.8 ; $P=.02$) and FEV₁ of -48.3 mL (95% CI, -90.8 to -5.9 ; $P=.03$), and those with HbA_{1c} concentrations of 6.0% to 6.4% had FVC of -139.6 mL (95% CI, -226.3 to -53.0 ; $P=.002$) and FEV₁ of -95.8 mL (95% CI, -164.7 to -26.8 ; $P=.01$). When we investigated the association of the prediabetic state (FPG 100-125 mg/dL or HbA_{1c} 5.7%-6.4%) with restrictive (FVC_{%pre}) or obstructive (FEV₁:FVC ratio) lung dysfunction according to quartile categories of these indices (Supplemental Table 2, available online at <http://www.mayoclinicproceedings.org>), individuals with

lower $FVC_{\%pre}$ were more likely to have elevated HbA_{1c} concentrations of 5.7% to 6.4% (OR, 1.37; 95% CI, 1.10-1.72; $P=.01$ for Q1; and OR, 1.26; 95% CI, 1.00-1.59; $P=.05$ for Q2). The OR for Q1 was significantly higher even after adjustment for other clinical markers (covariates in multivariate model in Table 2) and FPG concentrations (Supplemental Table 2, available online at <http://www.mayoclinicproceedings.org>). We did not observe significantly increased ORs for impaired FPG in individuals with low $FVC_{\%pre}$.

Lung Dysfunction and Risk of Development of Type 2 Diabetes

When we prospectively investigated whether there was an association of the 4 spirometry indices with the risk of development of diabetes, we observed a graded association between lower levels of restrictive lung dysfunction and the incidence of diabetes, although the association was substantially attenuated after adjustment for baseline HbA_{1c} values (Table 3). Results using the fully adjusted model (model 8) found that a 1-L decrease in FVC or FEV_1 was associated with an HR of 1.46 (95% CI, 1.15-1.85; $P=.002$) or HR of 1.56 (95% CI, 1.17-2.07; $P=.003$) for development of diabetes. A 10-point decrease in either $FVC_{\%pre}$ or $FEV_{1\%pre}$ was associated with an increase in the HR of 16% (95% CI, 4%-30%; $P=.01$), respectively. We observed fundamentally the same results when incident cases of diabetes were indicated by self-reported clinician-diagnosed diabetes regardless of the glycemic state (incident diabetes definition B in Table 3) or when we investigated findings of individuals with available data on cumulative exposures of pack-years of smoking ($n=4386$) (data not shown).

Lower quartile categories of the 4 spirometry indices were associated with higher HRs of incident diabetes in age-adjusted and multivariate FPG-adjusted models ($P<.001$ for trend for both models) (Table 2). We found that the trend of increasing HRs in lower categories of the spirometry indices was attenuated after adjustment for HbA_{1c} . However, lower quartile categories of FEV_1 and $FEV_{1\%pre}$ were still significantly associated with increased HRs even after adjustment for HbA_{1c} and other risk factors. Compared with the highest quartile (Q4), lower FEV_1 categories were associated with an HR of 1.79 (95% CI, 1.10-2.91; $P=.02$) for Q1 or HR of 1.86 (95% CI, 1.16-2.98; $P=.01$) for Q2 of developing diabetes. Likewise, those with lower $FEV_{1\%pre}$ (Q1 and Q2) had a 1.73-fold (95% CI, 1.14-2.62; $P=.01$) or a 1.76-fold (95% CI, 1.15-2.69; $P=.01$) increased risk for diabetes (multivariate HbA_{1c} -adjusted in Table 2). We observed no significant association across categories of the $FEV_1:FVC$ ratio and increased risk of diabetes.

DISCUSSION

According to our study results, lung dysfunction, in particular as measured using FEV_1 , was a significant and strong risk factor for development of type 2 diabetes in apparently healthy Japanese men. Restrictive lung dysfunction was more prevalent in individuals with elevated HbA_{1c} concentrations than in those with impaired FPG concentrations, and the association between lung dysfunction and risk of developing diabetes was attenuated by chronic non-diabetic hyperglycemia. However, the subsequent risk of development of diabetes in those with low FEV_1 or $FEV_{1\%pre}$ cannot be fully explained by this association.

Cross-sectional analyses that investigated the relationship between lung dysfunction and dysglycemia in individuals without diabetes found conflicting results.^{4,12-14} In the Rancho Bernardo Study,¹² FPG concentrations were significantly and negatively correlated with FEV_1 and FVC in elderly men without diabetes (diabetes indicated by FPG ≥ 140 mg/dL or 2-hour postchallenge glucose concentration ≥ 200 mg/dL or a history of physician-diagnosed diabetes), although no significant association was found between these variables and 2-hour postchallenge concentration. Results of the Framingham Offspring Cohort study also found an association of a higher concentration of FPG with lower than predicted values for FVC and FEV_1 .¹³ In individuals without diabetes in the Atherosclerosis Risk in Communities Study, Yeh et al⁷ reported a significant negative association of FPG and fasting insulin concentrations with $FVC_{\%pre}$. However, a prospective cohort study by Engström and Janzon³ did not find a significant association between FPG and FVC in the baseline analysis. According to analysis of data using results of the oral glucose tolerance test from the Third National Health and Nutrition Examination Survey,¹⁴ it was suggested that higher concentrations of HbA_{1c} , plasma insulin, C-peptide, and insulin resistance were associated with impaired lung function; nonetheless, elevated FPG concentrations were not associated with lung dysfunction. A study of 848 Japanese men with suspected impaired glucose metabolism found that high FPG and high HbA_{1c} concentrations were associated with $FVC_{\%pre}$.²³ However, no association of lung function with glucose and HbA_{1c} values was found in African American men with normal glucose tolerance.²⁴ In the present study of Japanese men without diabetes, we found a stronger association of lung function indices with HbA_{1c} than with FPG concentrations. Although we cannot determine the reasons for this finding from our observational study, because HbA_{1c} measurements reflect glycemic exposure over the previous 2 to 3 months that would include the influence of post-

TABLE 2. Association Between Measures of Pulmonary Function and Risk of Incident Type 2 Diabetes in Men^a

Measure of pulmonary function	Quartile				P value for trend
	1	2	3	4	
FVC (L)					
Quartile range	≤3.89	3.90-4.31	4.32-4.74	≥4.75	
No. of subjects	1328	1322	1371	1325	
No. of cases	83	58	40	33	
Age-adjusted HR (95% CI)	2.02 (1.31-3.13)	1.60 (1.03-2.47)	1.09 (0.69-1.73)	1.00 (Ref)	<.001
P value	.002	.04	.72	NA	
Multivariate FPG-adjusted HR (95% CI) ^b	2.12 (1.37-3.29)	1.23 (0.78-1.92)	1.21 (0.76-1.93)	1.00 (Ref)	<.001
P value	.001	.37	.43	NA	
Multivariate HbA _{1c} -adjusted HR (95% CI) ^b	1.44 (0.93-2.23)	1.30 (0.84-2.01)	1.00 (0.63-1.60)	1.00 (Ref)	.05
P value	.10	.24	.98	NA	
FEV ₁ (L)					
Quartile range	≤3.05	3.06-3.42	3.43-3.78	≥3.79	
No. of subjects	1307	1393	1325	1321	
No. of cases	83	65	40	26	
Age-adjusted HR (95% CI)	2.61 (1.60-4.26)	2.16 (1.36-3.46)	1.46 (0.89-2.39)	1.00 (Ref)	<.001
P value	<.001	.001	.14	NA	
Multivariate FPG-adjusted HR (95% CI) ^b	2.29 (1.41-3.71)	1.74 (1.08-2.79)	1.28 (0.77-2.11)	1.00 (Ref)	<.001
P value	.001	.02	.34	NA	
Multivariate HbA _{1c} -adjusted HR (95% CI) ^b	1.79 (1.10-2.91)	1.86 (1.16-2.98)	1.33 (0.80-2.19)	1.00 (Ref)	.01
P value	.02	.01	.27	NA	
FVC _{%pre} (%)					
Quartile range	≤95.7	95.8-103.8	103.9-111.6	≥111.7	
No. of subjects	1342	1330	1338	1336	
No. of cases	75	54	44	41	
Age-adjusted HR (95% CI)	1.89 (1.29-2.77)	1.42 (0.94-2.13)	1.18 (0.77-1.81)	1.00 (Ref)	<.001
P value	.001	.09	.45	NA	
Multivariate FPG-adjusted HR (95% CI) ^b	1.83 (1.24-2.71)	1.42 (0.94-2.14)	1.08 (0.70-1.66)	1.00 (Ref)	.001
P value	.002	.10	.74	NA	
Multivariate HbA _{1c} adjusted HR (95% CI) ^a	1.39 (0.95-2.05)	1.17 (0.77-1.76)	1.03 (0.67-1.58)	1.00 (Ref)	.06
P value	.09	.46	.89	NA	
FEV _{1%} pre (%)					
Quartile range	≤88.7	88.8-96.3	96.4-104.0	≥104.1	
No. of subjects	1327	1345	1345	1329	
No. of cases	75	64	42	33	
Age-adjusted HR (95% CI)	2.24 (1.49-3.37)	2.01 (1.32-3.07)	1.35 (0.85-2.13)	1.00 (Ref)	<.001
P value	<.001	.001	.20	NA	
Multivariate FPG-adjusted HR (95% CI) ^b	2.22 (1.46-3.38)	2.15 (1.40-3.30)	1.54 (0.97-2.45)	1.00 (Ref)	<.001
P value	<.001	<.001	.07	NA	
Multivariate HbA _{1c} -adjusted HR (95% CI) ^b	1.73 (1.14-2.62)	1.76 (1.15-2.69)	1.25 (0.79-1.99)	1.00 (Ref)	.004
P value	.01	.01	.33	NA	
FEV ₁ :FVC ratio (%)					
Quartile range	≤75.8	75.9-79.9	80.0-83.0	≥83.1	
No. of subjects	1335	1270	1420	1321	
No. of cases	52	61	58	43	

(continued)

(continued)

TABLE 2. Continued

Measure of pulmonary function	Quartile				P value for trend
	1	2	3	4	
Age-adjusted HR (95% CI)	0.90 (0.59-1.38)	1.27 (0.86-1.89)	1.18 (0.79-1.75)	1.00 (Ref)	.67
P value	.64	.23	.42	NA	
Multivariate FPG-adjusted HR (95% CI) ^b	0.95 (0.63-1.45)	1.09 (0.73-1.63)	1.13 (0.76-1.68)	1.00 (Ref)	.75
P value	.83	.66	.55	NA	
Multivariate HbA _{1c} -adjusted HR (95% CI) ^b	0.98 (0.64-1.50)	1.10 (0.74-1.63)	1.11 (0.75-1.65)	1.00 (Ref)	.90
P value	.93	.65	.61	NA	

^aCI = confidence interval; FEV₁ = forced expiratory volume in the first second of expiration; FEV_{1%pre} = FEV₁ for predicted values; FPG = fasting plasma glucose; FVC = forced vital capacity; FVC_{%pre} = FVC for predicted values; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio; NA = not available; Ref = reference value.

^bMultivariate: age, parental history of diabetes, physical activity, smoking status (never, former, current), body mass index, hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or medical treatment), log-transformed triglycerides, and high-density lipoprotein cholesterol.

prandial hyperglycemia, elevated HbA_{1c} concentrations might have a stronger relationship to impaired lung function than FPG concentrations that reflect just a moment in a single day.

In the prospective analyses, we found that restrictive lung function measures of FVC, FVC_{%pre}, FEV₁, and FEV_{1%pre}, rather than the obstructive lung function measure of the FEV₁:FVC ratio, were more likely to be associated with development of diabetes, although adjustment for elevated HbA_{1c} concentrations at baseline attenuated the association of restrictive lung dysfunction and diabetes risk. Our results are generally consistent with those of other studies that offered prospective data on the risk of diabetes and lung dysfunction as assessed using spirometry indices.³⁻¹⁰ Possible explanations for the association between lung dysfunction and increased risk of diabetes would include hypoxia-induced insulin resistance,^{25,26} chronic inflammation,²⁷⁻³¹ and the influence of low birth weight in early life. Low birth weight was associated with worse adult lung function³² and increased risk of diabetes.^{33,34} Another possible mechanism would be an association between lower levels of physical activity and lung dysfunction.³⁵ Recent prospective studies have suggested that restrictive impairment of lung function was associated with incident diabetes, which was partially explained by traditional and metabolic risk factors and inflammation⁹ or by obesity and inflammation.¹⁰ Restrictive lung dysfunction due to chest wall abnormality is commonly seen in individuals with moderate obesity. However, we observed that the association between low pulmonary function and the risk of diabetes was minimally attenuated after adjustment for body mass index and metabolic factors including hypertension and lipid concentrations. In the present study, we found that low lung function was associated with the prediabetic state as assessed by an elevated HbA_{1c} value

and that impaired pulmonary function was significantly predictive of the development of diabetes regardless of baseline dysglycemia. In contrast, we observed no association between obstructive lung dysfunction and increased risk of diabetes, which was consistent with results reported previously.³⁻¹⁰ Although the reasons have not yet been clarified, in individuals with restrictive lung dysfunction, FEV₁, FVC, and total lung capacity are reduced, but FEV₁:FVC ratios are usually normal. Inasmuch as the FEV₁ of predicted values correlates with the amount of physical activity that a subject can sustain, restrictive lung dysfunction with a relatively low FEV_{1%pre} might be a more sensitive marker for prediction of diabetes than restrictive lung dysfunction assessed using the FEV₁:FVC ratio. Although the severity of lung function abnormality based on FEV_{1%pre} was considered to be within low normal levels in this study, the lowest 2 quartile categories of FEV_{1%pre} were associated with development of diabetes in Japanese men.

Lung dysfunction is attracting great interest as a complication of diabetes.^{1,2} Because lung dysfunction as part of the prediabetic state has not been fully elucidated, our findings would contribute to a greater understanding of the association between lung function and chronic hyperglycemia as risk factors for diabetes in individuals without diabetes. Further studies will be needed to investigate whether introducing lung function measures into a prediction model that includes other predictors, as has been investigated in past studies,³⁶⁻³⁸ would lead to a more accurate prediction of subsequent diabetes.

The strength of the present study was the large sample size with follow-up data over a long period. Several limitations must be considered. First, because the present study included only men, the results cannot be extrapolated to women. Also, we cannot deny the possibility of selection bias because data were provided only for those who underwent

TABLE 3. Hazard Ratios for Development of Type 2 Diabetes Indicated by Definitions A and B^a

Model	FVC ^b		FEV ₁ ^b		FVC _{%pre} ^c		FEV _{1%} pre ^c		FEV ₁ :FVC ratio ^c	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Incident diabetes: definition A ^d										
Unadjusted	1.94 (1.58-2.39)	<.001	2.10 (1.67-2.64)	<.001	1.27 (1.14-1.42)	<.001	1.25 (1.12-1.40)	<.001	1.14 (0.93-1.40)	.19
Base ^e	1.67 (1.32-2.11)	<.001	1.80 (1.36-2.40)	<.001	1.25 (1.12-1.39)	<.001	1.22 (1.10-1.35)	<.001	0.97 (0.78-1.20)	.76
Body mass index ^f	1.63 (1.29-2.06)	<.001	1.72 (1.29-2.29)	<.001	1.24 (1.12-1.38)	<.001	1.21 (1.09-1.34)	.001	0.95 (0.76-1.19)	.68
Smoking ^g	1.63 (1.29-2.07)	<.001	1.69 (1.27-2.25)	<.001	1.24 (1.12-1.38)	<.001	1.20 (1.07-1.33)	.001	0.92 (0.73-1.15)	.47
Metabolic ^h	1.58 (1.24-2.01)	<.001	1.65 (1.24-2.21)	.001	1.22 (1.09-1.36)	<.001	1.18 (1.06-1.32)	.002	0.95 (0.76-1.19)	.65
Fasting plasma glucose ⁱ	1.76 (1.39-2.24)	<.001	1.99 (1.49-2.67)	<.001	1.28 (1.14-1.42)	<.001	1.28 (1.14-1.43)	<.001	1.05 (0.84-1.32)	.65
HbA _{1c} ^j	1.37 (1.08-1.74)	.01	1.40 (1.05-1.85)	.02	1.16 (1.04-1.29)	.01	1.13 (1.01-1.26)	.03	0.96 (0.77-1.20)	.72
Fully adjusted ^k	1.46 (1.15-1.85)	.002	1.56 (1.17-2.07)	.003	1.16 (1.04-1.30)	.01	1.16 (1.04-1.30)	.01	1.02 (0.81-1.29)	.85
Incident diabetes: definition B ^l										
Unadjusted	2.00 (1.42-2.82)	<.001	2.42 (1.65-3.53)	<.001	1.17 (0.98-1.41)	.09	1.23 (1.03-1.48)	.02	1.42 (1.04-1.95)	.03
Base ^e	1.54 (1.04-2.26)	.03	1.86 (1.16-2.99)	.01	1.15 (0.97-1.36)	.12	1.19 (1.00-1.41)	.05	1.18 (0.83-1.67)	.36
Body mass index ^f	1.52 (1.03-2.24)	.04	1.82 (1.13-2.92)	.01	1.15 (0.96-1.36)	.13	1.18 (0.99-1.40)	.06	1.16 (0.82-1.66)	.40
Smoking ^g	1.52 (1.03-2.25)	.04	1.78 (1.10-2.87)	.02	1.15 (0.96-1.37)	.13	1.17 (0.98-1.39)	.08	1.12 (0.78-1.60)	.54
Metabolic ^h	1.50 (1.02-2.22)	.04	1.81 (1.12-2.91)	.02	1.14 (0.96-1.36)	.14	1.18 (0.99-1.40)	.07	1.17 (0.82-1.67)	.38
Fasting plasma glucose ⁱ	1.63 (1.10-2.43)	.02	2.09 (1.29-3.41)	.003	1.18 (0.98-1.41)	.08	1.25 (1.04-1.49)	.02	1.29 (0.90-1.86)	.17
HbA _{1c} ^j	1.34 (0.90-1.99)	.15	1.54 (0.96-2.49)	.08	1.09 (0.91-1.30)	.36	1.12 (0.94-1.34)	.20	1.16 (0.81-1.67)	.43
Fully adjusted ^k	1.43 (0.96-2.13)	.08	1.72 (1.06-2.79)	.03	1.10 (0.92-1.32)	.29	1.16 (0.96-1.39)	.12	1.23 (0.84-1.78)	.29

^aCI = confidence interval; FEV₁ = forced expiratory volume in the first second of expiration; FEV_{1%}pre = FEV₁ for predicted values; FVC = forced vital capacity; FVC_{%pre} = FVC for predicted values; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio.

^bEach 1-L lower increment.

^cEach 10-point lower increment.

^dDefinition A: incidence of diabetes indicated by self-reported clinician diagnosis, HbA_{1c} ≥6.5% or fasting plasma glucose concentration ≥126 mg/dL.

^eAdjusted for age, parental history of diabetes, and physical activity.

^fAdjusted using model 2 criteria and body mass index.

^gAdjusted using model 3 criteria and smoking status (never, former, current).

^hAdjusted using model 3 criteria and hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or medical treatment), log-transformed triglycerides, and high-density lipoprotein cholesterol.

ⁱAdjusted using model 3 criteria and fasting plasma glucose concentration.

^jAdjusted using model 3 criteria and HbA_{1c}.

^kFully adjusted using criteria from all models.

^lDefinition B: incidence of diabetes indicated by self-reported clinician diagnosis.

the health examinations, because those individuals might pay more attention to their medical care than those not having such checkups. Further investigations in different populations will be needed to confirm our findings. Second, data on the oral glucose tolerance test were not available to enable a diagnosis of diabetes; therefore, underestimation of incident cases of type 2 diabetes is a possibility. In addition, we did not have data on inflammatory markers, which have been reported to be associated with both lung dysfunction^{29,30} and the incidence of diabetes.^{39,40} Further studies are needed to clarify the underlying mechanisms for the association be-

tween lung dysfunction and risk of diabetes. Such studies should include data on insulin resistance, insulin secretion, and other clinical markers during the development of diabetes.

CONCLUSION

Although the inverse association between lung function and risk of diabetes was attenuated by the influence of chronic glycemic exposure within a nondiabetic range, relatively low restrictive lung dysfunction, rather than obstructive dysfunction, is

an independent risk factor for development of diabetes in apparently healthy Japanese men.

ACKNOWLEDGMENTS

We thank the late Professor and Director Kinori Kosaka, MD, PhD, who established the foundation for the TOPICS project and was always the foremost pillar of spiritual support for the TOPICS project. We also thank Ms Satomi Fukuya for secretarial assistance.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>.

Abbreviations and Acronyms: CI = confidence interval; FEV₁ = forced expiratory volume in the first second of expiration; FEV_{1%pre} = FEV₁ for predicted values; FPG = fasting plasma glucose; FVC = forced vital capacity; FVC_{%pre} = FVC for predicted values; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio; OR = odds ratio

Grant Support: This work was supported in part by the Ministry of Health, Labour and Welfare, Japan. Dr Sone and Ms Heianza are recipients of a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science. The sponsor had no role in the design and conduct of the study.

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