BMJ open
accessible medical research

Cross-sectional and prospective study of the association between lung function and prediabetes

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To cite: Yamane T, Yokoyama A, Kitahara Y, *et al*. Cross-sectional and prospective study of the association between lung function and prediabetes. *BMJ Open* 2013;**3**:e002179. doi:10.1136/bmjopen-2012-002179

▸ Prepublication history for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2012-002179).

Received 12 October 2012
Revised 10 December 2012
Accepted 21 January 2013

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ABSTRACT

Objectives: A growing body of evidence suggests that there is a relationship between impaired lung function and the risk of developing diabetes mellitus (DM). However, it is not known if this reflects a causal effect of lung function on glucose metabolism. To clarify the relationship between lung function and the development of DM, we examined the incidence of newly diagnosed prediabetes (a precursor of DM) among subjects with normal glucose tolerance (NGT) at baseline.

Design: Primary analysis of an occupational cohort with both cross-sectional and longitudinal data (follow-up duration mean±SD: 28.4±6.1 months).

Setting and participants: Data were analysed from 1058 men in a cross-sectional study and from 560 men with NGT in a longitudinal study.

Outcomes and methods: Impaired lung function (per cent predicted value of forced vital capacity (%FVC) or per cent value of forced expiratory volume 1 s/FVC (FEV_1/FVC ratio)) in relation to the ratio of prediabetes or DM in a cross-sectional study and development of new prediabetes in a longitudinal study. NGT, prediabetes including impaired glucose tolerance (IGT) and increased fasting glucose (IFG) and DM were diagnosed according to 75 g oral glucose tolerance tests.

Measurements and main results: %FVC at baseline, but not FEV_1/FVC ratio at baseline, was significantly associated with the incidences of DM and prediabetes. Among prediabetes, IGT but not IFG was associated with %FVC. During follow-up, 102 subjects developed prediabetes among those with NGT. A low %FVC, but not FEV_1/FVC ratio, was predictive of an increased risk for development of IGT, but not of IFG.

Conclusions: Low lung volume is associated with an increased risk for the development of prediabetes, especially IGT, in Japanese men. Although there is published evidence for an association between chronic obstructive pulmonary disease and DM, prediabetes is not associated with the early stage of COPD.

ARTICLE SUMMARY

Article focus

- We hypothesised that lung function is associated with the development of impaired glucose metabolism. To investigate this, the data of an occupational cohort were analysed from 1058 men in a cross-sectional study and from 560 men with normal glucose tolerance (NGT) in a longitudinal study.

Key messages

- Low lung volume was significantly associated with the incidence of prediabetes or diabetes mellitus (DM) in both cross-sectional and longitudinal studies.
- Low lung volume is an independent risk factor for a particular type of prediabetes, impaired glucose tolerance rather than impaired fasting glucose. Our results suggested that prediabetes is not associated with the early stage of COPD, although there are published evidences for an association between COPD and DM.

Strengths and limitations of this study

- This is the first study that prospectively examined the incidence of newly diagnosed prediabetes among subjects with NGT at baseline. There are several limitations including that the subjects were limited to Japanese men and our occupational cohort may possibly be healthier than the general population.

INTRODUCTION

Accumulating evidence suggests that there is a close relationship between impaired lung function and diabetes mellitus (DM). Population-based studies have demonstrated associations between both obstructive and restrictive lung impairment and insulin resistance or DM.[1–9] A representative obstructive lung disease, chronic obstructive pulmonary disease (COPD), is now well known to be associated with a variety of comorbidities, including DM.[10–13] However, an accelerated decline of lung function has been observed in patients with DM.[14] The incidence rates of COPD, asthma, lung fibrosis and pneumonia

are greater in patients with DM than in those without DM.[15] The incidence of death from COPD is also increased in DM.[16]

The metabolic stage between normal glucose homeostasis and DM is called prediabetes, which the WHO divides into impaired glucose tolerance (IGT) and increased fasting glucose (IFG).[17] Both IFG and IGT are the established risk factors for DM.[18] The Diabetes Prevention Program Research Group[15] found that about 30% of subjects with prediabetes developed DM during 3–5 years of follow-up. IFG and IGT are also risk factors for cardiovascular disease (CVD), relationships that are not confounded by the development of DM.[19 20] Subjects with prediabetes also have higher incidence rates of microvascular complications, including neuropathy, retinopathy and nephropathy, than do those with normal glucose tolerance (NGT).[21 22]

We reported previously that smokers with airflow limitation had subclinical atherosclerosis as evidenced by carotid intima-media thickness (CIMT).[12] Although we excluded subjects with DM, the prediabetic state may influence the association, since prediabetes per se was accompanied by a modest but significant increase in the risk for developing CVD, as described above. However, there is no information regarding the association between lung function and prediabetes. Therefore, we explored the incidence of newly diagnosed prediabetes among selected subjects with NGT to further elucidate the nature of the relationship between lung function and the development of DM.

METHODS

Subjects

The subjects were recruited from 1218 men who attended the Nippon Telegraph and Telephone West Corporation Chugoku Health Administration Center for general health checkups between April 1999 and March 2006. One hundred and sixty subjects were excluded, because they did not meet the following inclusion criteria: (1) between 40 and 59 years of age at the first examination, and able to perform both a 75 g oral glucose tolerance test (OGTT) and adequate spirometric measurements (146 subjects excluded); (2) no known respiratory disease (14 excluded). Data from the remaining 1058 subjects were used for a baseline cross-sectional analysis. For the longitudinal study, subjects were restricted to those who had NGT (365 excluded), and could be followed up for more than 20 months (133 excluded). The remaining 560 subjects were included. Among these subjects, 77 were receiving medication for hypertension, 43 for dyslipidaemia and 11 for hyperuricaemia. The distributions of these subjects among the quartiles of percent predicted value of %FVC and percent value of 1 s/FVC (FEV_1/FVC ratio) were not significantly different.

The study was approved by the Ethical Committee of Kochi University.

75 g oral glucose tolerance test

DM and prediabetes were diagnosed according to the 2003 criteria of the WHO.[17] Subjects with prediabetes were classified into two categories: isolated IFG and IGT. Isolated IFG was defined as a fasting plasma glucose level of 6.1–6.9 mmol/l and a 2 h postload plasma glucose level of <7.8 mmol/l; and IGT was defined by a fasting plasma glucose level of <7.0 mmol/l and a 2 h postload plasma glucose level of 7.8–11.1 mmol/l. Blood samples were collected after a 10 h fast, and then 2 h after a 75 g oral glucose load.

Fasting insulin was measured by an enzyme immunoassay (Dainabot, Tokyo, Japan) with an intra-assay coefficient of variation of 3.1–4.4%. The homeostasis model assessment (HOMA) formula, (fasting insulin (mU/l)×fasting glucose (mmol/l))/22.5, was used to calculate the insulin resistance score.

Pulmonary function test

Pulmonary function was measured using a spirometer (Chest HI-801; Chest Co., Tokyo, Japan) by an experienced technician according to the recommendations of the American Thoracic Society.[23] The Japanese reference values were used.[24]

Statistical analysis

Statistical analysis was carried out using SPSS, V.18.0 (SPSS Japan Inc, Tokyo, Japan). Statistical comparisons of the baseline characteristics of each group were performed using either the χ-square test or one-way analysis of variance (ANOVA). Comparisons among the groups were performed by using post-hoc Tukey test. In the cross-sectional study, logistic regression models were used to estimate the relevant ORs. In the longitudinal study, the HR of each covariate for the risk of development of prediabetes with 95% CI was calculated using the Cox hazard model. Tests for a linear trend across increasing categories of spirometric indices were conducted by treating the categories as continuous variables in a model. In all analyses, $p<0.05$ was taken to indicate statistical significance.

RESULTS

Baseline analysis

At baseline, our study population (n=1058) consisted of 693 normal subjects, 93 with isolated IFG, 167 with IGT and 105 with DM. To examine the relationship between lung function parameters and impaired glucose metabolism, the subjects were divided into quartiles according to baseline %FVC and the FEV_1/FVC ratio. Some parameters, including age, body mass index (BMI), systolic blood pressure and total cholesterol, differed significantly among the quartiles (table 1). After adjustment for these parameters, impaired glucose metabolism was significantly associated with %FVC ($p<0.001$), but not with the FEV_1/FVC ratio ($p=0.80$). Specifically, IGT ($p=0.04$) and DM ($p=0.008$), but not isolated IFG ($p=0.28$), were associated with %FVC (table 2).

Table 1 Baseline characteristics of subjects with NGT, isolated IFG, IGT and DM in the cross-sectional study

	NGT	Isolated IFG	IGT	DM	p Value
Number of subjects	693	93	167	105	
Current smokers (%)	48	42	45	50	0.54
Age (years)	49.5±5.5	50.9±5.3*	51.1±5.3**	52.2±4.7***	<0.001
Height (cm)	169.9±5.7	168.8±5.8	169.1±6.0	168.4±5.0*	0.03
BMI (kg/m^2)	23.1±2.5	23.9±3.1**	24.6±2.8***	24.8±3.2***	<0.001
Systolic BP (mm Hg)	126.4±16.3	135.1±16.4***	135.9±18.2***	140.2±16.3***	<0.001
Pack-year smoking	30.5±15.6	38.0±22.6*	31.1±17.3	38.0±18.5**	0.002
FEV_1/FVC (%)	80.1±7.0	79.6±7.8	80.9±7.4	79.4±8.5	0.36
%FVC	97.9±14.2	96.5±12.9	92.0±13.3***	89.2±15.7***	<0.001
Fasting glucose (mmol/l)	5.3±0.4	6.3±0.2***	5.9±0.5***	8.1±1.6***	<0.001
120 min glucose (mmol/l)	5.7±1.0	6.5±0.8***	8.8±0.8***	12.4±4.0***	<0.001
HbA1c (%)	5.10±0.33	5.34±0.36***	5.37±0.41***	6.57±1.20***	<0.001
HOMA-R	1.08±0.56	1.91±2.23**	1.56±0.88***	2.33±1.41***	<0.001
C reactive protein (mg/l)	0.11±0.29	0.09±0.14	0.14±0.28	0.18±0.46	0.13
T-chol (mg/dl)	202.1±32.6	210.0±28.7*	209.5±36.3*	214.8±32.2***	<0.001

Values are numbers, percentages (%) or means ±SD.
*p<0.05.
**p<0.01.
***p<0.001 vs NGT.
BMI, body mass index; BP, blood pressure; CRP, C reactive protein; DM, diabetes mellitus; HbA1c, glycated haemoglobin; HOMA-R, homeostasis model assessment of insulin resistance; IFG, increased fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T-chol, total cholesterol.

Frequencies of newly diagnosed prediabetes in subjects with NGT

After the observation period (mean±SD: 28.4 ±6.1 months), there were 44 subjects with isolated IFG and 58 with IGT among those previously categorised as NGT (n=560), but no subject developed DM. As shown in table 3, there were significant differences in several parameters at baseline, including height, BMI, systolic blood pressure and %FVC, but not in FEV_1/FVC ratio.

Table 2 ORs*(95% CI) of prediabetes and DM according to the quartiles of %FVC† or FEV_1%‡ in the cross-sectional study

	I	II	III	IV	p for trend
IFG					
%FVC	1.0	4.60 (1.29 to 16.39)	2.03 (0.53 to 7.79)	2.57 (0.69 to 9.60)	0.06
FEV_1/FVC	1.0	1.00 (0.32 to 3.12)	1.39 (0.49 to 3.93)	1.81 (0.67 to 4.90)	0.53
IGT					
%FVC	1.0	1.35 (0.57 to 3.19)	2.18 (1.02 to 4.05)	2.59 (1.17 to 5.69)	0.04
FEV_1/FVC	1.0	0.60 (0.35 to 1.15)	0.62 (0.37 to 1.16)	0.50 (0.30 to 1.02)	0.12
IFG or IGT					
%FVC	1.0	2.18 (1.08 to 4.42)	2.09 (1.04 to 4.18)	2.55 (1.28 to 5.09)	<0.001
FEV_1/FVC	1.0	0.56 (0.31 to 1.07)	0.63 (0.35 to 1.14)	0.65 (0.36 to 1.17)	0.29
DM					
%FVC	1.0	3.77 (1.29 to 11.03)	1.28 (0.41 to 3.99)	2.50 (0.87 to 7.16)	0.02
FEV_1/FVC	1.0	2.08 (0.72 to 5.99)	3.05 (1.12 to 8.31)	2.13 (0.76 to 6.00)	0.18
IFG or IGT, or DM					
%FVC	1.0	3.32 (1.71 to 6.42)	2.04 (1.06 to 3.94)	3.33 (1.74 to 6.38)	<0.001
FEV_1/FVC	1.0	0.74 (0.40 to 1.35)	0.98 (0.56 to 1.75)	0.84 (0.48 to 1.49)	0.70

*OR was adjusted for age, BMI, pack-year smoking, systolic BP and T-chol.
†%FVC quartile; I (highest group) (≥104.2%), II (96.0%≤%FVC<104.2%), III (86.4%≤%FVC<96.0%), IV (lowest group) (%FVC<86.4%).
‡FEV_1/FVC quartile; I (highest group) (≥85.0), II (81.1%≤FEV_1/FVC<85.0%), III (76.5%≤FEV_1/FVC<81.1%), IV (lowest group) (FEV_1/FVC<76.5%).
BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; IFG, impaired fasting glucose; IFG, increased fasting glucose; IGT, impaired glucose tolerance; T-chol, total cholesterol.

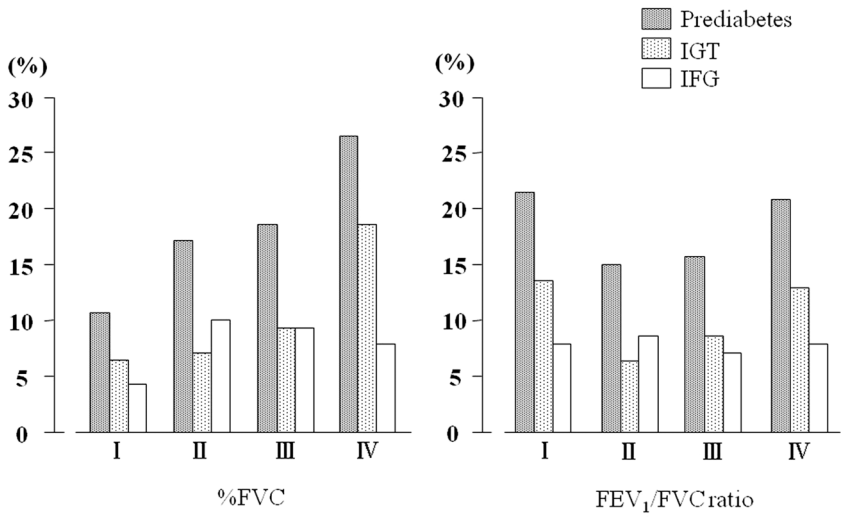

Figure 1 Incidences of newly diagnosed prediabetes, isolated IFG and impaired glucose tolerance (IGT) according to quartiles of % FVC and the FEV_1/FVC ratio. The incidence of prediabetes was significantly associated with %FVC, but not with the FEV_1/FVC ratio (p=0.01). Among subjects with prediabetes, lower %FVC was significantly associated with a higher incidence of IGT (p=0.04), but not of IFG (p=0.47).

Lung function parameters were divided into quartiles according to baseline %FVC and the FEV_1/FVC ratios. Among the quartiles the parameters, including age, BMI and systolic blood pressure, were significantly different (data not shown). Both in the crude model and following adjustment by age, BMI, pack-year smoking and systolic blood pressure, the development of prediabetes occurred significantly more frequently in the lowest quartile of % FVC, but not in that of the FEV_1/FVC ratio (table 4). Among prediabetes, IGT, but not isolated IFG, was significantly associated with %FVC, as in the baseline cross-sectional analysis (table 4; figure 1).

DISCUSSION

In the baseline cross-sectional study, we found that a low %FVC, but not a low FEV_1/FVC ratio, was significantly associated with increased prevalences of prediabetes and DM. As lung function might be impaired by DM, a causal effect of lung function on DM could not be established by these data. Therefore, we also explored prospectively the effect of lung function on the development of newly diagnosed prediabetes in the population with normal glucose metabolism, as evidenced by the results of an OGTT. We found that reduced lung volume (%FVC), but not airflow limitation (FEV_1/FVC ratio), was significantly associated with the future development of prediabetes.

This study demonstrated that IGT, but not IFG, was closely associated with lower lung volume in both cross-sectional and longitudinal settings. Our finding was supported by previous studies conducted in an Asian population with relatively low BMI but high smoking

Table 3 Baseline characteristics of subjects who remained NGT, developed isolated IFG and IGT in the longitudinal study.

	NGT	Isolated IFG	IGT	p Value
Number of subjects	458	44	58	
Current smokers (%)	48	30*	50	0.05
Age (years)	49.3±5.7	50.2±4.4	50.5±4.9	0.14
Height (cm)	169.9±5.6	170.2±4.9	167.1±6.7**	0.01
BMI (kg/m^2)	23.0±2.5	23.8±2.3*	23.7±3.0*	0.04
Systolic BP (mm Hg)	125.4±16.7	130.5±16.9*	129.3±14.5	0.048
Pack-year smoking	29.9±15.6	31.1±12.1	30.1±18.5	0.97
FEV_1/FVC (%)	80.1±7.1	79.7±6.3	79.9±7.9	0.95
%FVC (%)	97.5±14.2	93.0±14.7*	90.0±16.0***	<0.001
Fasting glucose (mmol/l)	5.3±0.4	5.6±0.2***	5.5±0.3**	<0.001
120 min glucose (mmol/l)	5.6±0.9	6.0±1.2	6.4±0.9***	<0.001
HbA1c (%)	5.07±0.33	5.31±0.37***	5.19±0.30*	<0.001
HOMA-R	1.04±0.53	1.19±0.61	1.31±0.64**	0.001
C reactive protein (mg/l)	0.10±0.23	0.18±0.42	0.16±0.30	0.26
T-chol (mg/dl)	201.4±34.5	205.3±27.1	212.5±28.6*	0.05
Duration (month)	28.6±6.2	28.5±5.1	27.6±5.6	0.13

Values are number, percentage (%) or mean±SD.
*p < 0.05.
**p<0.01.
***p<0.001 vs NGT.
BMI, body mass index; BP, blood pressure; CRP, C reactive protein; HOMA-R, homeostasis model assessment of insulin resistance; IFG, increased fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T-chol, total cholesterol.

Table 4 HRs (95% CI) for development of isolated IFG or IGT according to the quartiles of %FVC*or FEV_1%†

	I	II	III	IV	p for trend
IFG					
%FVC					
Model 1	1.0	0.85 (0.38 to 1.92)	0.81 (0.36 to 1.79	1.96 (0.71 to 5.26)	0.31
Model 2	1.0	1.07 (0.48 to 2.39)	1.35 (0.60 to 3.03)	0.54 (0.20 to 1.49)	0.32
FEV_1/FVC					
Model 1	1.0	0.96 (0.42 to 2.17)	1.20 (0.51 to 2.86)	0.98 (0.43 to 2.27)	0.95
Model 2	1.0	0.99 (0.43 to 2.31)	0.84 (0.35 to 2.00)	1.04 (0.45 to 2.47)	0.96
IGT					
%FVC					
Model 1	1.0	1.96 (1.00 to 3.85)	2.63 (1.27 to 5.56)	3.03 (1.43 to 6.67)	0.006
Model 2	1.0	2.22 (1.02 to 3.88)	2.26 (1.07 to 4.78)	2.74 (1.26 to 5.98)	0.02
FEV_1/FVC					
Model 1	1.0	2.13 (0.96 to 4.76)	1.67 (0.81 to 3.45)	1.03 (0.54 to 1.96)	0.15
Model 2	1.0	2.09 (0.92 to 4.72)	1.69 (0.81 to 3.52)	1.11 (0.57 to 2.16)	0.10
IFG or IGT					
%FVC					
Model 1	1.0	2.13 (0.93 to 3.03)	1.85 (1.03 to 3.57)	2.63 (1.43 to 4.76)	0.01
Model 2	1.0	1.48 (0.89 to 2.44)	1.38 (0.82 to 2.34)	2.40 (1.30 to 4.44)	0.04
FEV_1/FVC					
Model 1	1.0	1.47 (0.84 to 2.56)	1.47 (0.85 to 2.56)	1.01 (0.61 to 1.69)	0.32
Model 2	1.0	1.47 (0.83 to 2.61)	1.47 (0.84 to 2.56)	1.09 (0.64 to 1.84)	0.21

*%FVC quartile; I (highest group) (≥106.0%), II (96.6%≤%FVC<106.0%) III (88.1%≤%FVC<96.6%), IV (lowest group) (%FVC<88.1%).
†FEV_1/FVC quartile; I (highest group) (≥85.0%), II (80.9%≤FEV_1/FVC<85.0%), III (76.0%≤FEV_1/FVC<80.9%), IV (lowest group) (FEV_1/FVC<76.0%).
IGT, impaired glucose tolerance; IFG, increased fasting glucose.
Model 1 denotes crude model and model 2, adjusted for age, BMI, pack-year smoking and systolic BP.

prevalence.[8 9] In addition, such association between lower lung function and impaired glucose metabolism was also demonstrated in Western populations with higher BMI but lower smoking prevalence, and the association had been shown to be independent of smoking or obesity (refs. [1–6], for review ref. [7]).

The mechanisms for the association are not clarified at present. It has been suggested that IGT is caused mainly by insulin resistance in the muscle, and IFG mainly by insulin resistance in the liver.[25] Reduced lung volume is associated with reduced maximum oxygen uptake, which may lead to poorer physical fitness and physical activity, and thus result in insulin resistance and DM.[26–28] This may explain why IGT is more closely associated with lung volume. Furthermore, poorer lung function in adulthood may be due to low birth weight or early-life malnutrition,[29 30] both of which have been reported to be associated with the development of diabetes.[31] Malnutrition as a neonate may be an important early cause of cardiac and metabolic disorders in adulthood as a consequence of fetal programming.[32 33]

This study had several limitations. The study population was limited to men, owing to the fact that sufficient female subjects were not available at the institute. The occupational cohort used in this study may not be representative of Japanese men in general. For example, the prevalence rates of hypertension and hyperlipidaemia in this cohort were 13% and 7%, respectively (data not shown). The National Health and Nutrition Examination Survey in Japan showed prevalence rate of these in general Japanese men aged 40–60 years, in general, were around 30% and 35%, respectively, suggesting that our occupational cohort may be healthier. Subjects taking medications, including simvastatin, which have been shown to lower the risk of impaired glucose metabolism were not excluded, although the distributions of %FVC and the FEV_1/FVC ratio in those taking drugs for hypertension, dyslipidaemia and hyperuricaemia were not significantly different from those of subjects not on such medication.

In conclusion, this study provides evidence for a prospective relationship between lung volume and the incidence of newly diagnosed prediabetes among subjects with normal glucose metabolism at baseline. Among subjects with prediabetes, the study also suggests that lung volume may be a risk factor for the development of IGT, which is mainly caused by insulin resistance in the

muscle, but not IFG, which is caused mainly by insulin resistance in the liver. Although there is published evidence for an association between COPD and DM, our results suggest that prediabetes is not associated with at least the early stage of COPD.

Acknowledgements The authors would like to thank the staff of Nippon Telegraph and Telephone West Corporation Chugoku Health Administration Center.

Contributors TY contributed to the collection of data, analysis and interpretation of data, and writing of the draft. AY contributed to the study design, analysis and interpretation of data, editing of the draft and acquisition of funding. YK and SM contributed to the collection of data and analysis, YH, NH and KY contributed to the collection and interpretation of data, and editing the draft. NK contributed to the analysis and interpretation of data, and editing of the draft. All authors read and approved the final manuscript.

Funding This work was supported in part by a grant-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 23390222 and 24659405), and a grant to the Respiratory Failure Research Group from the Ministry of Health, Labor and Welfare, Japan.

Competing interests None.

Patient consent Obtained.

Ethics approval The Ethical Committee of Kochi University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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