



# LUND UNIVERSITY

## Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study.

Engström, Gunnar; Hedblad, Bo; Nilsson, P; Wollmer, Per; Berglund, Göran; Janzon, Lars

*Published in:*  
Journal of Internal Medicine

*DOI:*  
[10.1046/j.1365-2796.2003.01138.x](https://doi.org/10.1046/j.1365-2796.2003.01138.x)

2003

[Link to publication](#)

*Citation for published version (APA):*  
Engström, G., Hedblad, B., Nilsson, P., Wollmer, P., Berglund, G., & Janzon, L. (2003). Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study. *Journal of Internal Medicine*, 253(5), 574-581. <https://doi.org/10.1046/j.1365-2796.2003.01138.x>

*Total number of authors:*  
6

### General rights

Unless other specific re-use rights are stated the following general rights apply:  
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00

# Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study

G. ENGSTRÖM<sup>1</sup>, B. HEDBLAD<sup>1</sup>, P. NILSSON<sup>2</sup>, P. WOLLMER<sup>3</sup>, G. BERGLUND<sup>2</sup> & L. JANZON<sup>1</sup>

From the Departments of <sup>1</sup>Community Medicine, <sup>2</sup>Medicine, and <sup>3</sup>Clinical Physiology, University of Lund, Malmö University Hospital, Malmö, Sweden

**Abstract.** Engström G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L (University of Lund, Malmö University Hospital, Malmö, Sweden). Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study. *J Intern Med* 2003; **253**: 574–581.

**Objectives.** To explore whether a reduced lung function is a risk factor for developing diabetes and insulin resistance (IR), and whether such relationship contributes to the largely unexplained association between lung function and incidence of cardiovascular disease (CVD).

**Design.** Forced vital capacity (FVC) was assessed at baseline. Incidence of diabetes and IR [according to the homeostasis model assessment (HOMA) model] was assessed in a follow-up examination after  $13.9 \pm 2.6$  and  $9.4 \pm 3.6$  years for men and women, respectively. After the follow-up examination, incidence of CVD (stroke, myocardial infarction or cardiovascular death) was monitored over 7 years.

**Setting.** Populations-based cohort study.

**Subjects.** Initially nondiabetic men ( $n = 1436$ , mean age 44.6 years) and women ( $n = 896$ , mean age 49.8 years).

**Results.** Prevalence of IR at the follow-up examination was 34, 26, 21 and 21%, respectively, for men in the first (lowest), second, third and fourth quartile of baseline FVC ( $P$  for trend  $<0.0001$ ). The corresponding values for women were 30, 29, 25 and 17%, respectively ( $P$  for trend  $<0.001$ ). Adjusted for potential confounders, the odds ratio (OR) for IR (per 10% increase in FVC) was 0.91 (CI: 0.84–0.99) for men and 0.89 (CI: 0.80–0.98) for women. FVC was similarly significantly associated with the incidence of diabetes (OR = 0.90, CI: 0.81–1.00), adjusted for sex and other confounders.

The incidence of CVD after the follow-up examination was significantly increased only amongst subjects with low FVC who had developed IR (RR = 1.7, CI: 1.02–2.7).

**Conclusion.** Subjects with a moderately reduced FVC have an increased risk of developing IR and diabetes. This relationship seems to contribute to the largely unexplained association between reduced lung function and incidence of CVD.

**Keywords:** diabetes, forced vital capacity, glucose, insulin resistance, spirometry.

## Introduction

Pulmonary dysfunction is one of the many clinical features associated with diabetes [1–7]. Cross-sectional studies have reported associations between insulin resistance (IR) and reduced lung function [8, 9]. The temporal and causal relationships of these associations are unclear. Reduced lung function is often considered to be a complication following diabetes mellitus [1–7]. However, some studies

suggest that a reduced lung function could be a risk factor for the development of IR [10] or diabetes [11]. Few researchers have explored this hypothesis. To our knowledge, there are no previous studies of these relationships in women.

A moderately reduced lung function has repeatedly been associated with an increased incidence of cardiovascular diseases (CVD) [12–14]. This association has remained significant after adjustments for smoking and other potential confounders. Similar

associations have been reported from studies of life-long nonsmokers [14]. The nature of this association is poorly understood. Whether associations between lung function and development of IR or diabetes contribute to the relationships between lung function and incidence of CVD is not known.

The first aim of this longitudinal study was to investigate whether reduced lung function is associated with future IR and diabetes in a large cohort of both men and women. Another aim was to study whether such relationship could contribute to the associations between reduced lung function and incidence of CVD.

## Subjects and methods

### *Baseline cohort*

Between 1974 and 1983, 22 444 men participated in the Malmö Preventive Study, a screening programme for detection of individuals with high risk for CVDs [15]. A total of 10 902 women were examined between 1977 and 1991. Participation rate was approximately 71%. Determination of forced vital capacity (FVC) was part of the programme for 20 100 nondiabetic men and 7433 nondiabetic women.

### *Follow-up cohort*

Between November 1991 and February 1994, a random 50% of the subjects who entered the ongoing Malmö Diet and Cancer study took part in an extended cardiovascular study, which included measurements of insulin and glucose levels [16, 17]. Of the subjects with complete information of glucose and insulin levels, 1436 men and 896 women had previously been examined with spirometry in the Malmö Preventive Study and were at that time nondiabetic. They constitute the sample of the present study. Mean age at the baseline examination was  $44.6 \pm 3.9$  years (range: 35–52) and  $49.8 \pm 5.6$  (range: 38–57) years, respectively, for men and women. Age at the follow-up examination was  $58.5 \pm 5.1$  and  $59.1 \pm 5.6$  years, respectively. A flow chart of the study population is presented in Fig. 1.

In order to assess the representativeness of the study cohort, the present sample was compared with the remaining subjects in the Malmö Preventive Study who were eligible for the present study (i.e.

subjects who were nondiabetic and had information on FVC at baseline and were invited to the follow-up examination). The differences between the study cohort and eligible subjects who did not enter the follow-up examination were small with respect to glucose (men:  $4.85 \pm 0.5$  vs.  $4.90 \pm 0.5$  mmol L<sup>-1</sup>, women:  $4.71 \pm 0.5$  vs.  $4.73 \pm 0.6$  mmol L<sup>-1</sup>) and FVC in percentage of predicted values (FVC%p, men:  $97 \pm 16$  vs.  $96 \pm 16\%$ ; women:  $110 \pm 18$  vs.  $108 \pm 19\%$ ). As expected, FVC%p was lower amongst men ( $n = 1131$ ) and women ( $n = 153$ ) who died before the follow-up examination than amongst those who survived (men:  $90 \pm 18$  vs.  $96 \pm 16\%$ ; women:  $104 \pm 21$  vs.  $109 \pm 19\%$ ).

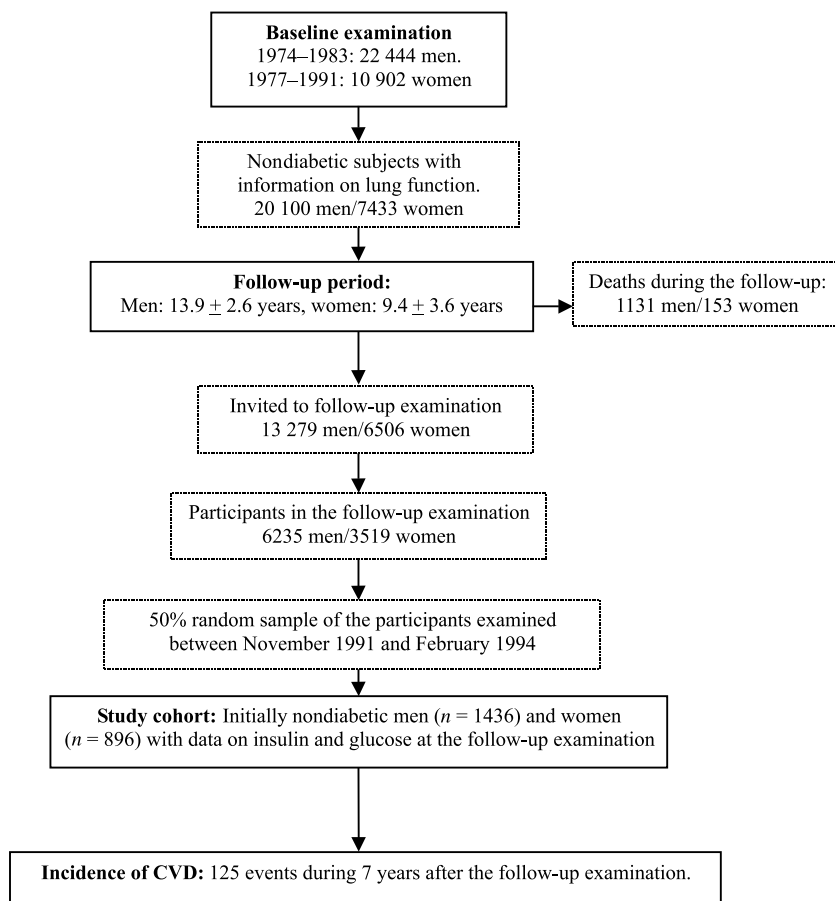
### *Clinical data and physical examinations*

A Spirotron apparatus (Drägerwerk AG, Lübeck, Germany) was used with the subjects in a standing position without noseclips. Specially trained nurses performed the tests. One acceptable manoeuvre, with respect to the subject's performance and co-operation, was required. The volumes were adjusted for age and height using equations from a reference population of nonsmoking Caucasians [18], and expressed as FVC%p values.

A questionnaire was used to assess smoking habits at baseline. Subjects were categorized into smokers (smoking daily) and nonsmokers. Tobacco consumption was categorized as daily consumption of 1–9, 10–19, and 20 cigarettes or more.

Physical activity was assessed by a questionnaire at the follow-up examination. Seventeen activities together with open alternatives were used to describe leisure-time physical activity [19]. For each type of physical activity, the participants were asked how many minutes per week they spent during each season. The average time was multiplied with an intensity factor to create a physical activity index [16]. The physical activity score was standardized, for men and women separately, to a mean ( $\pm$ SD) of 1.00 ( $\pm$ 1.00). For 70 subjects with missing data on physical activity, the mean activity level was coded in order to keep these individuals available for the multivariate analysis.

Height and weight was measured whilst the subject wore light indoor clothing and was without shoes. Body mass index (BMI) was calculated as weight/height<sup>2</sup> (kg m<sup>-2</sup>). Waist and hip circumferences were measured at the follow-up



**Fig. 1** Flowchart of the study population.

examination and the waist to hip ratio (WHR) was calculated.

#### *Laboratory analyses*

Blood samples for the determination of insulin and venous whole blood glucose were drawn after an overnight fast. Insulin was measured with a nonspecific radioimmunoassay [20]. The limit for detection of insulin was 3 mIU L<sup>-1</sup>. Intra- and inter-assay coefficients of variation were 5 and 8%, respectively. Information on insulin was available for all subjects at follow-up and for 511 men at baseline.

#### *Definition of insulin resistance and diabetes*

The homeostasis model assessment (HOMA) formula, fasting insulin × fasting glucose/22.5, was used to calculate the IR score [21]. Subjects who belonged to the top quartile (i.e. >2.35 for men, >1.88 for women) were considered to have IR according to the proposed definition from the

European Group for the study of Insulin Resistance (EGIR) [22]. The relationships between the HOMA values and other cardiovascular risk factors have been reported previously [16].

Diabetes was defined as fasting venous whole blood glucose ≥6.1 mmol L<sup>-1</sup> or known diabetes. All subjects with diabetes at baseline were excluded.

#### *Cardiovascular events after the follow-up examination*

Incidence of cardiovascular events was monitored from the follow-up examination until 31 December 1999. A cardiovascular event was defined as fatal or nonfatal myocardial infarction [code 410 according to the International Classification of Diseases, 9th version, (ICD-9), or deaths caused by ischaemic heart disease, codes 412 and 414], stroke (ICD-9 codes 430, 431, 434, 436) or death from cardiovascular causes (ICD-9 codes 390–459). The Swedish Cause of Death Register, the Swedish Hospital Discharge register [23, 24] and the Stroke Register of Malmö [25] were used for case retrieval.

### Statistics

Analysis of variance and logistic regression were used to assess the relationships between baseline FVC%p and cardiovascular risk factors at baseline and follow-up. Log-transformed values of glucose, insulin and HOMA were used because of the skewed distributions. A general linear model was used to adjust the association between log glucose and quartile of FVC%p for age, smoking and BMI. A Cox proportional hazards model was used to study incidence of cardiovascular events in relation to categories of lung function and IR and to adjust the relationships for potential confounders.

## Results

### *FVC and cardiovascular risk factors at baseline*

The relationships between FVC%p and age, BMI, smoking and fasting glucose at baseline are presented for men and women in Tables 1 and 2. FVC%p was inversely associated with smoking. Mean age was similar in all quartiles of FVC%p, both in men and women. At baseline, FVC%p was inversely associated with fasting glucose amongst women (Table 2). However, this association was no longer significant ( $P = 0.10$ ) after adjustments for age, smoking and BMI. No association between FVC%p and glucose at baseline was found for men (Table 1).

### *FVC at baseline in relation to IR and glucose at follow-up*

Glucose and insulin at follow-up were significantly and inversely associated with baseline FVC%p. Both in men and women, FVC%p was significantly associated with IR at follow-up (Tables 1 and 2).

The associations between baseline FVC%p and IR at follow-up remained significant after adjustments for potential confounders (Table 3). The association with future IR was similar when subjects with diabetes at follow-up were excluded from the analysis (all: OR = 0.89, CI: 0.83–0.96; men: OR = 0.90, CI: 0.82–0.99; women: OR = 0.89, CI: 0.81–0.98). The results were virtually identical after further adjustments for the treatment of hypertension at baseline and follow-up. Exclusion of the small number treated with oral steroids (seven men, five women) did not change the results.

Information on fasting insulin values at baseline was available in a subgroup of 511 men. The association between baseline FVC%p and future IR was similar in this subgroup when HOMA at baseline (log-transformed) was included in the model instead of log glucose (OR = 0.84, CI: 0.73–0.98).

The relationships between FVC%p and future IR was significant both amongst nonsmokers (OR = 0.91, CI: 0.83–0.99) and smokers (OR = 0.89, CI: 0.81–0.98), adjusted for the covariates listed in Table 3.

The relationships between FVC%p and IR were also, in addition to all the covariates listed in Table 3, adjusted for baseline levels of systolic blood pressure, cholesterol and triglycerides. The adjusted OR was essentially unchanged (OR = 0.91, CI: 0.86–0.98).

### *FVC at baseline in relation to diabetes at follow-up*

A total of 144 men (10.0%) and 42 women (4.7%) developed diabetes during the follow-up. The incidence of diabetes was significantly and inversely associated with baseline FVC%p (Tables 1 and 2). FVC%p remained significantly associated with incidence of diabetes after adjustments for sex and other potential confounders (Table 3).

### *Cardiovascular events after the follow-up examination*

Incidence of cardiovascular events after the follow-up examination was monitored over a mean follow-up of  $6.9 \pm 0.88$  years. The highest cardiovascular event rate was found in subjects with FVC%p below median who had developed IR (Table 4). The increased cardiovascular event rates in this group remained significant after adjustments for several potential confounders (RR = 1.7, CI: 1.02–2.7) (Table 4). The results were essentially similar after the exclusion of the subjects who had developed diabetes at the follow-up examination (RR = 1.6, CI: 0.94–2.8). A low FVC%p was not associated with cardiovascular events in the absence of IR.

## Discussion

Reduced pulmonary function is often considered a complication following diabetes [1–7]. Few have studied whether a reduced lung function could be a

**Table 1** Characteristics at screening and at follow-up of 1436 initially nondiabetic men by quartile of height and age-adjusted forced vital capacity (FVC) (Q4 = highest FVC)

| Men   | Height and age-adjusted FVC at baseline |                 |                  |                  | P for trend |
|---|---|-----------------|------------------|------------------|-------------|
|   | Q1<br>(n = 359)                         | Q2<br>(n = 359) | Q3<br>(n = 359)  | Q4<br>(n = 359)  |             |
| FVC (% of predicted)                            | <88                                     | 88–98           | 99–107           | >107             |             |
| Characteristics at screening                    |   |                 |                  |                  |             |
| Age at screening (years)                        | 44.9 ± 3.8                              | 44.6 ± 3.8      | 44.0 ± 4.1       | 44.7 ± 3.6       | 0.17        |
| BMI (kg m <sup>-2</sup> )                       | 24.9 ± 3.5                              | 24.4 ± 3.1      | 24.2 ± 2.6       | 24.6 ± 2.6       | 0.09        |
| Glucose (mmol L <sup>-1</sup> )                 | 4.8 (+0.7)                              | 4.9 (+0.7)      | 4.8 (+0.6)       | 4.8 (+0.6)       |             |
| Glucose (log-transformed)                       | 1.57 ± 0.10                             | 1.58 ± 0.10     | 1.58 ± 0.10      | 1.57 ± 0.11      | 0.22        |
| Insulin (mIU L <sup>-1</sup> ) (n) <sup>a</sup> | 8.5 (+9.0) (142)                        | 9.0 (+10) (124) | 7.0 (+7.0) (122) | 8.0 (+7.0) (123) |             |
| Insulin (log-transformed)                       | 2.03 ± 0.70                             | 2.07 ± 0.72     | 1.99 ± 0.64      | 2.04 ± 0.64      | 0.89        |
| Current smoking n (%)                           | 187 (52)                                | 147 (41)        | 145 (40)         | 102 (28)         | <0.001      |
| Characteristics at follow-up                    |   |                 |                  |                  |             |
| Follow-up (years)                               | 14.0 ± 2.0                              | 13.9 ± 1.9      | 13.8 ± 2.0       | 13.8 ± 2.4       | 0.11        |
| Weight increase (kg)                            | 5.4 ± 6.5                               | 4.7 ± 6.0       | 5.4 ± 5.5        | 5.4 ± 4.8        | 0.61        |
| Waist–hip ratio                                 | 0.95 ± 0.06                             | 0.94 ± 0.06     | 0.94 ± 0.05      | 0.94 ± 0.05      | 0.03        |
| Physical activity score                         | 0.91 ± 0.97                             | 1.05 ± 1.04     | 0.94 ± 0.90      | 1.10 ± 1.07      | 0.06        |
| Incidence of diabetes n (%)                     | 53 (16)                                 | 39 (11)         | 22 (6.2)         | 30 (8.5)         | 0.0003      |
| Glucose (mmol L <sup>-1</sup> )                 | 5.2 (+0.8)                              | 5.1 (+0.8)      | 5.0 (+0.6)       | 5.0 (+0.7)       |             |
| Glucose (log-transformed)                       | 1.67 ± 0.19                             | 1.65 ± 0.17     | 1.63 ± 0.12      | 1.64 ± 0.16      | <0.001      |
| Insulin (mIU L <sup>-1</sup> )                  | 8.0 (+6.0)                              | 7.0 (+5.0)      | 7.0 (+4.0)       | 7.0 (+4.0)       |             |
| Insulin (log-transformed)                       | 2.09 ± 0.61                             | 1.96 ± 0.60     | 1.90 ± 0.52      | 1.93 ± 0.62      | 0.0001      |
| Insulin resistance n (%)                        | 122 (34)                                | 95 (26)         | 74 (21)          | 75 (21)          | <0.0001     |

Median (+interquartile range), mean ± SD or n (%).

<sup>a</sup>Baseline insulin values available in 511 men.**Table 2** Characteristics at screening and at follow-up of 896 initially nondiabetic women in relation to height and age-adjusted quartile of forced vital capacity (FVC) (Q4 = highest FVC)

| Women                           | Height and age-adjusted FVC at baseline |                 |                 |                 | P for trend |
|---------------------------------|---|-----------------|-----------------|-----------------|-------------|
|                                 | Q1<br>(n = 224)                         | Q2<br>(n = 224) | Q3<br>(n = 224) | Q4<br>(n = 224) |             |
| FVC (% of predicted)            | <100                                    | 100–109         | 110–122         | >122            |             |
| Characteristics at screening    |   |                 |                 |                 |             |
| Age at screening (years)        | 50.4 ± 5.5                              | 49.4 ± 5.5      | 49.5 ± 5.7      | 49.7 ± 5.7      | 0.26        |
| BMI (kg m <sup>-2</sup> )       | 23.6 ± 3.9                              | 23.9 ± 3.8      | 23.9 ± 3.7      | 23.2 ± 3.1      | 0.26        |
| Glucose (mmol L <sup>-1</sup> ) | 4.7 (+0.6)                              | 4.8 (+0.7)      | 4.7 (+0.7)      | 4.6 (+0.7)      |             |
| Glucose (log-transformed)       | 1.56 ± 0.10                             | 1.55 ± 0.12     | 1.53 ± 0.11     | 1.54 ± 0.10     | 0.01        |
| Current smoking n (%)           | 116 (52)                                | 82 (37)         | 63 (28)         | 57 (26)         | <0.001      |
| Characteristics at follow-up    |   |                 |                 |                 |             |
| Follow-up (years)               | 8.9 ± 3.9                               | 9.5 ± 3.6       | 9.7 ± 3.5       | 9.4 ± 3.3       | 0.12        |
| Weight increase (kg)            | 4.5 ± 6.1                               | 4.8 ± 5.8       | 4.4 ± 5.3       | 4.3 ± 5.1       | 0.60        |
| Waist–hip ratio                 | 0.79 ± 0.05                             | 0.79 ± 0.05     | 0.79 ± 0.05     | 0.78 ± 0.05     | 0.12        |
| Physical activity score         | 1.00 ± 0.98                             | 0.98 ± 0.95     | 1.04 ± 1.12     | 0.97 ± 0.94     | 0.85        |
| Incidence of diabetes n (%)     | 15 (6.8)                                | 11 (5.0)        | 12 (5.4)        | 4 (1.8)         | 0.02        |
| Glucose (mmol L <sup>-1</sup> ) | 4.9 (+0.6)                              | 4.85 (+0.7)     | 4.8 (+0.65)     | 4.7 (+0.5)      |             |
| Glucose (log-transformed)       | 1.61 ± 0.16                             | 1.59 ± 0.13     | 1.59 ± 0.16     | 1.56 ± 0.10     | 0.001       |
| Insulin (mIU L <sup>-1</sup> )  | 6.0 (+5.0)                              | 7.0 (+4.0)      | 6.0 (+5.0)      | 6.0 (+4.0)      |             |
| Insulin (log-transformed)       | 1.85 ± 0.56                             | 1.91 ± 0.57     | 1.83 ± 0.58     | 1.74 ± 0.54     | 0.019       |
| Insulin resistance n (%)        | 68 (30)                                 | 65 (29)         | 57 (25)         | 38 (17)         | 0.0008      |

Median (+interquartile range), mean ± SD or n (%).

**Table 3** Odds ratios (95% confidence intervals) for diabetes and insulin resistance at follow-up in relation to a 10% increase in baseline forced vital capacity (FVC) in percentage of predicted values (FVC%p) in men and women who initially were nondiabetic

|       | Dependent variable |                   |
|-------|--------------------|-------------------|
|       | Insulin resistance | Diabetes          |
| All   | 0.90 (0.84–0.96)** | 0.90 (0.81–1.00)* |
| Men   | 0.91 (0.84–0.99)*  | 0.92 (0.81–1.03)  |
| Women | 0.89 (0.80–0.98)*  | 0.87 (0.71–1.08)  |

Adjusted for sex, age at screening, follow-up time, smoking, tobacco consumption, body mass index, log glucose at baseline, waist–hip ratio (at follow-up), physical activity (at follow-up).

\* $P < 0.05$ , \*\* $P < 0.01$ .

risk factor for future IR and diabetes. The results of the present study show that FVC is associated with the development of diabetes and IR as assessed by the HOMA model. Furthermore, subjects with FVC below median who developed IR showed an increased risk of cardiovascular events. An increased incidence of diabetes and IR could contribute to the largely unexplained relationships between lung function and incidence of CVD.

Our results are in accordance with previous studies of male subjects in which low FVC was associated with development of IR or diabetes [10, 11, 26]. To our knowledge, there is no previous study of the associations between lung function and future diabetes or IR in women. This is also the first time the association between lung function and IR has been related to subsequent outcome. IR has previously been associated with an increased incidence of CVDs [17, 27]. In the present study, the increased risk of cardiovascular events was, however, mainly observed amongst subjects with

IR who had showed a low FVC. Low FVC was not associated with cardiovascular events in the absence of IR. The results suggest that an increased risk of future IR and diabetes partially explains the relationship between lung function and incidence of CVDs. It is however likely that other risk factors contribute to this relationship as well. For example, a reduced lung function has been associated with future increase in systolic and diastolic blood pressure [28] and with the occurrence and prognostic significance of ventricular arrhythmia [29].

There are some methodological issues that need to be considered. The association between FVC and IR was adjusted for glucose at baseline. The results were similar when the associations were adjusted for HOMA values at baseline in a subgroup of 511 men. Differences in insulin sensitivity at baseline cannot explain the associations between FVC and future IR. Smoking is a major cause of reduced lung function. However, whether smoking is associated with the development of IR is controversial [30, 31]. Smoking was taken into account in the analysis, and the relationships between FVC and future IR were consistent in smokers and nonsmokers. It is very unlikely that smoking explains the associations between FVC and IR.

Another question is the validity of the HOMA model as a measure of IR. The correlations between the HOMA model and the hyperinsulinaemic–euglycaemic clamp technique, which is generally considered to be the golden standard in measurements of IR, have been about 0.7 in nondiabetic subjects [32]. It has been demonstrated that IR, as assessed by the HOMA model, is a predictor of diabetes [33]. As assessments of IR with the clamp technique is not feasible in most epidemiological

**Table 4** Cardiovascular events after the follow-up examination in relation to FVC and insulin resistance

|                                      | No insulin resistance |                 | Insulin resistance |                |
|--------------------------------------|-----------------------|-----------------|--------------------|----------------|
|                                      | High FVC              | Low FVC         | High FVC           | Low FVC        |
| N (men/women)                        | 920 (566/354)         | 818 (504/314)   | 246 (152/94)       | 348 (214/134)  |
| Cardiovascular events ( <i>n</i> )   | 40                    | 33              | 16                 | 36             |
| MI/stroke/other CV deaths            | 23/16/1               | 17/16/0         | 7/8/1              | 19/15/2        |
| Events/1000 person-years             | 6.4                   | 5.9             | 9.7                | 15.7           |
| Age- and sex-adjusted RR             | 1.00                  | 0.92 (0.58–1.5) | 1.5 (0.82–2.6)     | 2.3 (1.5–3.6)  |
| Risk factor adjusted RR <sup>a</sup> | 1.00                  | 0.85 (0.53–1.3) | 1.2 (0.68–2.3)     | 1.7 (1.02–2.7) |

<sup>a</sup>Adjusted for sex and age, smoking, cholesterol, systolic blood pressure, waist–hip ratio, physical activity, history of myocardial infarction or stroke at the follow-up examination.

High FVC: forced vital capacity above median; low FVC: below median; RR, relative risk (95% confidence interval); MI, myocardial infarction; CV, cardiovascular.

studies, the HOMA model is considered to be a useful surrogate method [34]. It could be questioned whether it is accurate to determine the occurrence of IR by a single test. However, misclassification of IR would, if anything, result in an underestimation of the associations as long as the error is unrelated to baseline FVC.

The measurement of FVC is another methodological issue. The protocol of the health examinations was developed several years before the commonly used guidelines for standardized spirometry were published [19, 35] and the lung function tests did not meet the standards of the statements. However, the associations between FVC and other cardiovascular risk factors in the present study are similar to those reported from other studies [13]. Random measurement errors would, if anything, reduce the risk estimates.

This study was limited to individuals who participated in both examinations. Both reduced lung function and IR have been associated with cardiovascular mortality [12–14, 17, 27, 29]. Mortality before the follow-up examination would therefore, if anything, reduce the observed associations. Nonparticipation in the follow-up examination is another potential cause of bias. The differences between the participants and eligible nonparticipants were however rather small with respect to FVC and glucose levels. We cannot claim that the sample is truly representative, and the results are thus based on the internal validity of the cohort. There is no reason to believe, however, that the results could not be extrapolated to the general population.

The causal associations between FVC and future IR can only be speculated about. FVC could be reduced for many different reasons and the pulmonary changes that precede IR may be different from those reported amongst patients with diabetes mellitus [5–7]. Inflammation is one factor that is associated with a reduced lung function. Studies of healthy subjects have reported associations between reduced lung function and increased levels of markers of inflammation [36, 37]. There is also a growing recognition of associations between the immune system and the metabolism of glucose and insulin. For example, a nested case–control study recently demonstrated that raised plasma levels of the acute phase reactant C-reactive protein is associated with future diabetes [38] and tumour necrosis factor- $\alpha$  may be important for the metabo-

lism of glucose and insulin [39]. Inflammation has also been associated with the development of atherosclerosis [40]. Hence, a systemic low-grade inflammation could be the link between reduced FVC, development of IR and subsequent CVD. Hypoxia or chronic pulmonary diseases are however unlikely explanations for the observed findings, as the present sample was from the general population, and very few of them had an abnormal FVC from a clinical perspective. The inverse relationship, i.e. that IR causes reduced FVC and thereby explains the results, also seems unlikely. There was a long time-period between the baseline and follow-up examinations and the results remained significant both after excluding subjects with diabetes at follow-up and after adjustments for glucose or HOMA levels at baseline.

It is concluded that a reduced FVC is associated with an increased risk of future IR and diabetes. This relationship could contribute to the largely unexplained association between reduced lung function and incidence of CVD.

### Conflict of interest statement

No conflict of interest was declared.

### Acknowledgements

The study was supported by grants from the Åke Wiberg foundation, the Swedish Society for Hypertension and the Swedish Council for Work Life and Social Research.

### References

- 1 Sandler M. Is the lung a 'target organ' in diabetes mellitus? *Arch Intern Med* 1990; **150**: 1385–8.
- 2 Davis TME, Knudman 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* 2000; **50**: 153–9.
- 3 Barrett-Connor E, Frette C. NIDDM, impaired glucose tolerance, and pulmonary function in older adults. *Diabetes Care* 1996; **19**: 1441–4.
- 4 Lange P, Groth S, Kastrup J *et al.* Diabetes mellitus, plasma glucose and lung function in a cross-sectional population study. *Eur Respir J* 1989; **2**: 14–9.
- 5 Schuyler MR, Niewoehner DE, Inkley SR, Kohn R. Abnormal lung elasticity in juvenile diabetes mellitus. *Am Rev Respir Dis* 1976; **113**: 37–41.
- 6 Marvisi M, Bartolini L, del Borrello P *et al.* Pulmonary function in non-insulin-dependent diabetes mellitus. *Respiration* 2001; **68**: 268–72.



- 7 Weynand B, Jonckheere A, Frans A, Rahier J. Diabetes mellitus induces a thickening of the pulmonary basal lamina. *Respiration* 1999; **66**: 14–9.
- 8 Burchfiel CM, Curb JD, Sharp DS *et al*. Distribution and correlates of insulin in elderly men. The Honolulu Heart Program. *Arterioscler Thromb Vasc Biol* 1995; **15**: 2213–21.
- 9 Lazarus R, Sparrow D, Weiss ST. Impaired ventilatory function and elevated insulin levels in nondiabetic males: the Normative Aging Study. *Eur Respir J* 1998; **12**: 635–40.
- 10 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* 1998; **12**: 641–5.
- 11 Engström G, Janzon L. Risk of developing diabetes is inversely related to lung function: a population-based cohort study. *Diabetic Med* 2002; **19**: 167–70.
- 12 Engström G, Hedblad B, Valind S, Janzon L. Increased incidence of myocardial infarction and stroke in hypertensive men with reduced lung function. *J Hypertens* 2001; **19**: 295–301.
- 13 Kannel WB, Hubert H, Lew EA. Vital capacity as a predictor of cardiovascular disease: The Framingham study. *Am Heart J* 1983; **105**: 311–5.
- 14 Hole DJ, Watt GCM, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996; **313**: 711–5.
- 15 Berglund G, Nilsson P, Eriksson KF *et al*. Long-term outcome of the Malmö preventive project: mortality and cardiovascular morbidity. *J Intern Med* 2000; **247**: 19–29.
- 16 Hedblad B, Nilsson P, Janzon L, Berglund G. Relation between insulin resistance and carotid intima-media thickness and stenosis in non-diabetic subjects. Results from a cross-sectional study in Malmö, Sweden. *Diabetic Med* 2000; **17**: 299–307.
- 17 Hedblad B, Nilsson P, Engström G, Berglund G, Janzon L. Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death. *Diabetic Med* 2002; **19**: 470–5.
- 18 Standardised lung function testing. Official statement of the European Respiratory Society. *Eur Resp J* 1993; **6** (Suppl. 16): 25–7.
- 19 Taylor HL, Jacobs DR Jr, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis* 1978; **31**: 741–55.
- 20 Thorell JI, Larson SM. *Radioimmunoassay and Related Techniques*. St Louis: CV Moseby Company, 1978; 205–11.
- 21 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–9.
- 22 Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for Study Insulin Resistance. *Diabetic Med* 1999; **16**: 442–3.
- 23 Engström G, Berglund G, Göransson M *et al*. Distribution and determinants of ischaemic heart disease in an urban population. A study from the myocardial infarction register in Malmö, Sweden. *J Intern Med* 2000; **247**: 588–96.
- 24 Värdering av diagnoskvaliten för akut hjärtinfarkt i patientregistret 1987 and 1995 [in Swedish]. *The National Board of Health and Welfare*, Stockholm, Sweden.
- 25 Engström G, Jerntorp I, Pessah-Rasmussen H, Hedblad B, Berglund G, Janzon L. Geographic distribution of stroke incidence within an urban population: relations to socioeconomic circumstances and prevalence of cardiovascular risk factors. *Stroke* 2001; **32**: 1098–103.
- 26 Eriksson KF, Lindgärde F. Poor physical fitness, and impaired early insulin response but late hyperinsulinaemia, as predictors of NIDDM in middle-aged Swedish men. *Diabetologia* 1996; **39**: 573–9.
- 27 Ruige JB, Assendelft WJJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and risk of cardiovascular disease. A meta-analysis. *Circulation* 1998; **97**: 996–1001.
- 28 Engström G, Wollmer P, Valind S, Hedblad B, Janzon L. Blood pressure increase between 55 and 68 years of age is inversely related to lung function: longitudinal results from the cohort study 'Men born in 1914'. *J Hypertens* 2001; **19**: 1203–8.
- 29 Engström G, Wollmer P, Hedblad B, Juul-Möller S, Valind S, Janzon L. Occurrence and prognostic significance of ventricular arrhythmia is related to pulmonary function: a study from 'Men born in 1914', Malmö, Sweden. *Circulation* 2001; **103**: 3086–91.
- 30 Henkin L, Zaccaro D, Haffner S *et al*. Cigarette smoking, environmental tobacco smoke exposure and insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *Ann Epidemiol* 1999; **9**: 290–6.
- 31 Eliasson B, Attvall S, Taskinen MR, Smith U. The insulin resistance syndrome in smokers is related to smoking habits. *Arterioscler Thromb* 1994; **14**: 1946–50.
- 32 Bonora E, Kiechl S, Willeit J *et al*. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. *Diabetes* 1988; **47**: 1643–9.
- 33 Haffner SM, Kennedy E, Gonzalez C, Stern MP, Miettinen H. A prospective analysis of the HOMA model. The Mexico City Diabetes Study. *Diabetes Care* 1996; **19**: 1138–41.
- 34 Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antonio Heart Study. *Diabetes Care* 1997; **20**: 1087–92.
- 35 American Thoracic Society. Snowbird workshop on standardization of spirometry. *Am Rev Respir Dis* 1979; **119**: 831–8.
- 36 Mendall MA, Strachan DP, Butland BK *et al*. C-reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. *Eur Heart J* 2000; **21**: 1584–90.
- 37 Engström G, Lind P, Hedblad B *et al*. Lung function and cardiovascular risk: relationship with inflammation-sensitive plasma proteins. *Circulation* 2002; **106**: 2555–60.
- 38 Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; **286**: 327–34.
- 39 Hotamisligil GS. Mechanisms of TNF-alpha-induced insulin resistance. *Exp Clin Endocrinol Diabetes* 1999; **107**: 119–25.
- 40 Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; **340**: 115–26.

Received 17 October 2002; revision received 13 January 2003; accepted 5 February 2003.

*Correspondence:* Gunnar Engström MD, PhD, Department of Community Medicine, Malmö University Hospital, S-20502 Malmö, Sweden (fax: +46 40336215; e-mail: gunnar.engstrom@smi.mas.lu.se).