Low lung function, sudden cardiac death and non-fatal coronary events in the general population

Suneela Zaigham,1 Karl-Fredrik Eriksson,2 Per Wollmer,1,3 Gunnar Engström1

ABSTRACT

Background Many of those who suffer from a first acute coronary event (CE) die suddenly during the day of the event, most of them die outside hospital. Poor lung function is a strong predictor of future cardiac events; however, it is unknown whether the pattern of lung function impairment differs for the prediction of sudden cardiac death (SCD) versus non-fatal CEs. We examined measures of lung function in relation to future SCD and non-fatal CE in a population-based study.

Methods Baseline spirometry was assessed in 28 584 middle-aged subjects, without previous history of CE, from the Malmö Preventive Project. The cohort was followed prospectively for incidence of SCD (death on the day of a first CE, inside or outside hospital) or non-fatal CE (survived the first day). A modified version of the Lunn McNeil’s competing risk method for Cox regression was used to run models for both SCD and non-fatal CE simultaneously.

Results A 1 SD reduction in forced expiratory volume in 1 s (FEV1) was more strongly associated with SCD than non-fatal CE even after full adjustment (FEV1; HR for SCD: 1.23 (1.15 to 1.31), HR for non-fatal CE 1.08 (1.04 to 1.13), p value for equal associations=0.002). Similar associations were found for forced vital capacity (FVC) but not FEV1/FVC. The results remained significant even in life-long never smokers (FEV1; HR for SCD: 1.34 (1.15 to 1.55), HR for non-fatal CE: 1.11 (1.02 to 1.21), p value for equal associations=0.036). Similar associations were seen when % predicted values of lung function measures were used.

Conclusions Low FEV1, is associated with both SCD and non-fatal CE, but consistently more strongly associated with future SCD. Measurement with spirometry in early life could aid in the risk stratification of future SCD.

INTRODUCTION

Sudden cardiac death (SCD) is an unexpected death of cardiac origin, occurring within 1 hour of onset of symptoms in witnessed cases or within 24 hours of being seen alive and well if un witnessed.1 Since there is usually incomplete information from witnesses in population-based settings, other operational definitions are frequently used, such as coronary deaths outside hospital or a fatal outcome during the day of the acute coronary event (CE) in individuals without any previous history of acute CEs. The typical pathophysiological sequence of events in the majority of cases is the onset of ventricular tachycardia, degenerating into ventricular fibrillation and finally to asystole.2 Coronary heart disease (CHD) is the underlying condition in approximately 70%–80% of SCD events,1,3,4 and in many cases, SCD is the first and only indication of heart disease.5 It has been thought of as an ‘epidemiological paradox’ since a large proportion of the absolute number of sudden cardiac death cases comes from those not considered to be high-risk individuals.4,6 The value of conventional cardiovascular risk markers to predict fatal arrhythmic events in individual subjects is low, and, therefore, a search for more specific markers of predicting fatal arrhythmias leading to SCD are needed.2 Although an association between low vital capacity (VC) and SCD has been proposed,7,8 there have not been many studies of the general population to explore this association further. Chronic obstructive pulmonary disease (COPD) has been associated with SCD,9 but few studies exist for pulmonary function in otherwise healthy individuals, as a marker of SCD. A
prospective population-based study in 2015 assessed impaired pulmonary function as a risk predictor for SCD in over 1000 middle-aged men and found that reduced lung function as measured by spirometry was a robust predictor of SCD; a finding that was also replicated in non-smokers. In an additional population-based study in Malmö, Sweden, it was found that in just under 5500 apparently healthy men with moderately reduced lung function, a higher case-fatality was found for future CE. One of the most striking findings was that lung function predicted the fatality of a CE when the men were comparatively young (mean age 47 years) and healthy, that is, many years before the CE took place itself.

Although poor lung function is a strong predictor of future cardiac events, it is unknown whether the pattern of lung function impairment differs for the prediction of SCD versus non-fatal CE, and which of the two outcomes are more strongly associated with poor lung function earlier in life.

In this study, we aim to assess if measures of spirometry are associated with future SCD and non-fatal CE using prospective data from a general population study in over 28500 participants.

METHODS

Study population

The study population consisted of subjects from the Malmö Preventive Project where middle-aged individuals were screened with an aim to offer preventative treatment to any identified high-risk individuals. Screening was carried out between 1974 and 1992 in 33 346 subjects (22 444 men and 10 902 women) (participation rate of over 70%). Complete birth cohorts for 1921–1949 were invited and self-administered questionnaires. Men were mostly screened between 1974 and 1982 and women between 1982 and 1992. The screening programme was approved and funded by the Health Service Authority of Malmö.

Subjects with prevalent CHD or cardiovascular disease (CVD) were excluded, which included a history of CEs or a history of stroke, based on self-reported questionnaire data or registers of hospital inpatients (n=182). Spirometry was performed in birth cohorts during most but not all screening periods (94% of men and 71% of women); however, individuals were not selected based on symptoms or disease. Subjects with missing information on spirometry were excluded (n=4389). Subjects with missing information on key covariates were excluded (n=147). Subjects with an erythrocyte sedimentation rate (ESR) ≥50 mm/hour were excluded as this could potentially indicate the presence of a specific inflammatory lung pathology (n=63). The final study population consisted of 28 584 subjects (20 939 men and 7645 women).

Patient and public involvement

Study participants were not involved in the study design and conduct, or the reporting and dissemination of the study findings.

Baseline examinations

Forced expiratory volume in 1s (FEV1) and forced VC (FVC) were measured using a spirotorn apparatus (Drägerwerk AG, Lübeck, Germany), carried out by trained nursing staff. Only one acceptable manoeuvre was required. FEV1, FVC and FEV1/FVC were standardised for age and height and published equations derived from linear regression of never smokers in the present cohort (online supplemental methods). Height (metres) was measured using a fixed stadiometer; weight (kg) was measured on a balance beam scale. Body mass index (BMI) was calculated as kg/m². Blood pressure (BP) (mm Hg) was measured after a 10 min rest in the supine position (two measurements taken and mean value recorded). Blood samples were taken after an overnight fast and analysed at the Department of Clinical Chemistry, Malmö University hospital. Information on smoking habits was assessed using a questionnaire, and based on their responses, participants were divided into current, former or never smokers.

Endpoint ascertainment

All individuals with a history of CE, according to self-report or patient registers, were excluded. SCD was defined as a fatal CE where death took place on the first day of the CE (within the first 24 hours), in individuals without a previous CE. This includes cases that died out of hospital. International Classification of Diseases (ICD) 8 and 9 codes included 410, 412 and 414; and ICD 10 codes I21, I24 and I25 were used. Cause of death was based on autopsy for 61% of the SCDs in this study. A non-fatal CE was defined as a CE with ICD 8 and 9 code 410 or ICD 10 code I21, which survived the first day. Data linkage with the National Cause of Death Registry, Swedish Hospital Discharge registry and the Malmö Myocardial Infarction Register was used to retrieve cases. All subjects were followed from the baseline examinations until the first non-fatal CE or fatal CE, death from other causes, emigration or mortality from other causes, whichever came first. During the entire follow-up period, the Swedish inpatient registry had been in operation in the south of Sweden, which became nationwide in 1987. Data from this registry have acceptable validity for epidemiological research.

Statistical analysis

All analyses were carried out using SPSS V.26 (IBM, Armonk, New York, USA) and Stata V.14.0. Cox regression models were run to obtain HRs for SCD and non-fatal CE per 1-SD change in lung function measures. Time from baseline examination to the first incident CE, SCD, emigration or mortality from other causes, whichever came first, was used. Adjustments were made for potential confounding factors (model 1: age, sex and height; model 2: age, sex, height, BMI, smoking status, prevalent diabetes, systolic BP and cholesterol). Time-dependent
covariate analysis was used to check proportional hazards assumption for all models. They were met for all except models for non-fatal outcomes per 1-SD decrease in FEV1, FEV1/FVC ratio and FVC (for FVC model 1 only). To further assess the proportional hazards for these models, we tested the assumptions using Kaplan Meier plots.

A modified version of the Lunn McNeil’s competing risks method for Cox regression was used to run models for both SCD and non-fatal CE simultaneously. The null hypothesis associated with the p value obtained from this method is that the lung function variable has the same association with SCD and non-fatal CE. This method has been described in detail elsewhere. In order to assess the effect of inflammation, models were additionally adjusted for ESR. To fully control for the effect of smoking, we carried out an analysis in life long never smokers (n=9947).

RESULTS
Subject characteristics are presented in Table 1. The mean age of participants was approximately 45 years. Almost half the cohort were current smokers; however, the known prevalence of COPD at baseline was low at 0.3%. Mean follow-up time was approximately 30 years.

Sudden cardiac death
There were 1609 SCD events over the follow-up period. Crude incident rates of SCD by quartiles of lung function measures are presented in Table 2 and online supplemental figure 1. Q1 (low lung function) had the highest rates of SCD (events per 1000 person-years). There was an increased adjusted risk of SCD per 1-SD decrease in FEV1 and FVC (L) (table 3), which remained significant after additionally adjusting for ESR (HR per 1-SD decrease in FEV1 and FVC (L): (1.21 (1.13 to 1.30) and 1.19 (1.11–1.28), respectively. Similar associations were seen using %predicted values of FEV1 and FVC (online supplemental table 1).

In lifelong never smokers (table 4 and online supplemental table 2), there was a strong-adjusted risk of SCD per 1-SD decrease in FEV1 and FVC (L) (HR: 1.34 (1.15

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Table 1  Baseline characteristics (n=28 584)  

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>44.6 (±7.2)</td>
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<tr>
<td>Gender (%, male)</td>
<td>73.3</td>
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<tr>
<td>Height (m)</td>
<td>1.74 (±0.09)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>24.4 (±3.5)</td>
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<td>Smoking status (%)</td>
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<tr>
<td>Current smokers</td>
<td>48.1</td>
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<tr>
<td>Former smokers</td>
<td>17.1</td>
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<tr>
<td>Never smokers</td>
<td>34.8</td>
<td></td>
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<tr>
<td>Prevalent diabetes (%)</td>
<td>3.1</td>
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<tr>
<td>Prevalent COPD (%)</td>
<td>0.3</td>
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<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.61 (±1.07)</td>
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<tr>
<td>ESR (mm/h)*</td>
<td>5.0 (3.0–8.0)</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
<td>126 (±15)</td>
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<tr>
<td>Lung function measurement</td>
<td></td>
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<tr>
<td>FEV1 (L)</td>
<td>3.28 (±0.82)</td>
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<tr>
<td>FEV1 (%predicted)</td>
<td>95.2 (±17.9)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FVC (L)</td>
<td>4.20 (±1.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (%predicted)</td>
<td>97.0 (±16.5)</td>
<td></td>
<td></td>
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<tr>
<td>FEV1/FVC</td>
<td>0.785 (±0.092)</td>
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<tr>
<td>FEV1/FVC (%predicted)</td>
<td>98.5 (11.4)</td>
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</tbody>
</table>

Data are presented as mean±SD unless otherwise stated. *Median values with 25th–75th percentiles for covariates with skewed distribution.

BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 2  Incident SCD and non-fatal CE by quartiles of lung function (n=28 584)  

<table>
<thead>
<tr>
<th>FEV1 (L)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n=28 584)</td>
<td>7454</td>
<td>6691</td>
<td>7584</td>
<td>6855</td>
</tr>
<tr>
<td>SCD events n (n per 1000 person-years)</td>
<td>518 (2.6)</td>
<td>405 (2.0)</td>
<td>405 (1.7)</td>
<td>281 (1.2)</td>
</tr>
<tr>
<td>Non-fatal CE n (n per 1000 person-years)</td>
<td>1093 (5.4)</td>
<td>994 (5.0)</td>
<td>1089 (4.6)</td>
<td>826 (3.6)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
</tr>
<tr>
<td>Subjects (n=28 584)</td>
<td>6950</td>
<td>6828</td>
<td>7283</td>
<td>7523</td>
</tr>
<tr>
<td>SCD events n (n per 1000 person-years)</td>
<td>435 (2.3)</td>
<td>414 (2.1)</td>
<td>424 (1.9)</td>
<td>336 (1.4)</td>
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<tr>
<td>Non-fatal CE n (n per 1000 person-years)</td>
<td>959 (5.0)</td>
<td>1017 (5.0)</td>
<td>1084 (4.8)</td>
<td>942 (3.8)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
</tr>
<tr>
<td>Subjects (n=28 584)</td>
<td>7155</td>
<td>7178</td>
<td>7130</td>
<td>7121</td>
</tr>
<tr>
<td>SCD events n (n per 1000 person-years)</td>
<td>508 (2.5)</td>
<td>397 (1.8)</td>
<td>358 (1.6)</td>
<td>346 (1.6)</td>
</tr>
<tr>
<td>Non-fatal CE n (n per 1000 person-years)</td>
<td>1089 (5.4)</td>
<td>1019 (4.6)</td>
<td>1020 (4.6)</td>
<td>874 (3.9)</td>
</tr>
</tbody>
</table>

CE, coronary events; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; Q, quartile; SCD, sudden cardiac death.
to 1.55) and 1.36 (1.16 to 1.59), respectively) and per 1-SD decrease in %predicted FEV$_1$ and FVC (HR: 1.23 (1.11 to 1.36) and 1.24 (1.12 to 1.38), respectively). After additionally adjusting for ESR in never smokers, results remained largely unchanged (results not shown).

**Incident non-fatal CE**

There were 4002 non-fatal CE during the follow-up period. Individuals with low lung function (Q1) had the highest rates of non-fatal CE (table 2, online supplemental figure 2). HR of non-fatal CE per 1-SD decrease in spirometry measures is shown in table 3. There was an increased adjusted risk of non-fatal CE per 1-SD decrease in FEV$_1$ and FVC (L), which remained significant after additionally adjusting for ESR (HR per 1-SD decrease in FEV$_1$ and FVC (L): 1.07 (1.02 to 1.12) and 1.06 (1.02 to 1.11), respectively. Similar associations were seen using %predicted values of FEV$_1$ and FVC (online supplemental table 1).

In life long never smokers (table 4), there was a strong adjusted risk of non-fatal CE per 1-SD decrease in FEV$_1$ and FVC (L) (HR: 1.11 (1.02 to 1.21)) and 1.16 (1.05 to 1.27), respectively) and per 1-SD decrease in %predicted FEV$_1$ and FVC (HR: 1.08 (1.02 to 1.15) and 1.10 (1.03 to 1.17), respectively, online supplemental table 2). After additionally adjusting for ESR in never smokers, results remained largely unchanged (results not shown).

**Comparing the risk of SCD events and incident non-fatal CE for baseline lung function**

An 1-SD reduction in FEV$_1$ and FVC was more strongly associated with SCD than non-fatal CE even after full adjustment (p value 0.0020 and 0.0055, respectively) (table 3), which remained significant even after further adjusting for ESR. Similar associations were seen using %predicted values of FEV$_1$ and FVC (online supplemental table 1). In life-long never smokers, a 1-SD reduction in FEV$_1$ remained more strongly associated with SCD than non-fatal CE (p value, 0.0380), which after further adjustment for ESR was borderline significant (p value, 0.05). Similar associations were seen using %predicted values of FEV$_1$ and FVC (online supplemental table 2), and after further adjustment for ESR, results remained borderline significant for FEV$_1$ %predicted (p value for equal associations—0.045).

An additional analysis in ever smokers (former and current smokers) showed broadly similar results to the main analysis, where FEV$_1$ and FVC (litres and %predicted values) were more strongly associated with SCD than non-fatal CE, even after full adjustments (online supplemental table 2).
with low lung function and optimise their treatment to further reduce the risk of SCD and non-fatal CE.

It has been found that left ventricular (LV) dysfunction is associated with an increased risk of SCD along with being associated with low FEV₁ and FVC. However, a reduced FVC has been associated with cardiac hospitalisations even after adjustments for left heart size and in those with normal LV ejection fraction (LVEF). Previous research nevertheless found that different patterns of loss of lung health in young adulthood are associated with specific cardiac phenotypes in middle age. A decline in FVC with a preserved FEV₁/FVC ratio was found to be associated with LV hypertrophy and diastolic dysfunction—a ‘hypertrophic, high output phenotype’ later in life, whereas a declining FEV₁ with decline in FEV₁/FVC was associated with decreased left heart chamber size and decreased cardiac output—a ‘small heart, low output phenotype’. There was no echocardiography information available in the present study, so we were unable to assess the role of subclinical heart failure in the relationship between low lung function and SCD. If this association is explained to some extent by the presence of heart failure, it would then be important to establish if it is independent of LVEF by assessing whether similar findings between reduced lung function and ventricular arrhythmias (VA) or SCD are also observed in those with diastolic dysfunction.

There is emerging evidence that arrhythmias contribute to the increased cardiovascular mortality in COPD. However, the pathophysiology that links COPD to fatal arrhythmias may indeed differ from that which links low lung function in the absence of pulmonary disease to fatal malignant arrhythmias. A study in the ‘Men Born in 1914’ cohort in Malmö, Sweden assessed the association between low levels of lung function and the occurrence and prognostic significance of VA. In 68-year-old men free from CVD, the occurrence of VA on 24-hour ambulatory ECG (24-hour ECG) was inversely associated with pulmonary function, and additionally the increased cardiac risk and mortality risk associated with VA were mainly limited to men with low FEV₁ %predicted or low FEV₁/VC. The Cardiovascular Health Study also used 24-hour ECG to assess the prevalence and correlates of cardiac arrhythmias in the elderly and reported significantly lower lung function in those with arrhythmias compared with those without. These studies support the hypothesis of VA as a potential link between lung function and SCD. To better understand underlying mechanisms, further studies are needed of the arrhythmic risk in individuals with poor lung function.

A corrected QT interval (QTc) of >440 ms is associated with a high risk of SCD, independently of age, sex, history of myocardial infarction, heart rate and medication use. The population-based Multi-Ethnic Study of Atherosclerosis found an inverse association between FEV₁ %, FVC %, FEV₁/FVC % and prolonged QTc. The results suggest that low lung function could be a risk factor for longer QTc in the general male population,
even in those without lung disease. Autonomic dysfunction associated with reduced lung function has been suggested as a potential mechanism for these findings.\textsuperscript{20} We did not have ECG information in the present study, so were unable to determine if the association between low lung function and SCD was explained by a prolonged cardiac repolarisation.

An additional explanation may include the association between lung function and atherosclerosis,\textsuperscript{30} which could be mediated through systemic inflammation and potentially increase the risk of VA and SCD. Although we attempt to take into the account the role of systemic inflammation by additionally adjusting the final models for ESR, we are aware that there is likely a residual effect of confounding from inflammation that could potentially effect the results. However, it unlikely that any residual confounding effect influenced the results of SCD more than non-fatal outcomes; therefore, it cannot explain the stronger association of low lung function with SCD compared with non-fatal CE.

**Limitations**
The study protocol was developed before the current guidelines for spirometry were developed. Therefore, no nose clips were used, and only one acceptable manoeuvre was required. All lung function measurements were prebronchodilator values. However, it has been thought that postbronchodilator measurements may not be necessary in studies assessing long-term outcomes.\textsuperscript{31} Due to the long follow-up time associated with prospective follow-up studies, there are many risk factors that would have changed over this period, such as smoking status, BMI, diagnosis of COPD/other comorbidities or the use of medications such as inhaled corticosteroids. However, we do not expect that the results were influenced by an increase in uptake of smoking over the follow-up period as prevalence of smoking in Sweden decreased over the duration of the study\textsuperscript{32} and is uncommon for non-smokers to start smoking in adulthood.\textsuperscript{33} Changing smoking habits should affect the risk of SCD and non-fatal CE in a similar way, and a systematic bias seems unlikely. It has been found that the burden of CVD in 50-year old men in Sweden has reduced over the last approximately 50 years,\textsuperscript{34} and although we expect this would be mirrored in the population of Malmö, it would if anything bias results towards the null.

It has generally been established that a greater proportion of the out-of-hospital deaths is directly caused by ventricular dysrhythmia rather than coronary thrombosis\textsuperscript{35} and FEV\textsubscript{1} could be a potentially useful tool in risk stratification for out of hospital SCD in the general population.\textsuperscript{36} We were unable to determine whether the fatal CEs were witnessed and, therefore, whether death occurred within the first hour of onset of symptoms. However, we are able to select cases of fatal CE that occurred on the day of an acute CE, which, therefore, fulfils the definition of unwitnessed SCD events and would also include both in and out of hospital SCD.

SCD is a devastating event with profound consequences for surviving family members.\textsuperscript{1} Prediction of SCD in the general population remains a challenge as the largest patient groups for SCD are those with the fewest known risk factors.\textsuperscript{37} This study is the first to directly compare the risk of SCD and non-fatal CE in the general population in relation to baseline lung function measures in both men and women.

**CONCLUSION**
Low FEV\textsubscript{1} is consistently more strongly associated with future SCD than incident non-fatal CE. Measurement with spirometry in early life could aid in the risk stratification of future SCDs, and, therefore, allow for early intervention to potentially reduce the risk of this devastating event.

**Contributors**
SZ, K-FE, PW and GE participated in study design, interpretation of data, drafting the manuscript and approved the final version of the manuscript. SZ performed the statistical analyses and prepared the first draft of the manuscript. All authors take responsibility for the integrity and accuracy of the work. The authors read and approved the final manuscript.

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**Competing interests**
PW reports grants from Swedish Heart and Lung Foundation during the conduct of the study, and personal fees from Chiesi Pharma, personal fees from GlaxoSmithKline, outside the submitted work. PW has a patent device and method for pulmonary function measurement issued.

**Patient consent for publication**
Not required.

**Ethics approval**
The Health Service Authority of Malmö approved and funded the screening programme. Linkage with the national cause of death and patient registers and ethical approval to study incidence of cardiopulmonary diseases and death was approved by the Regional Ethics Committee at Lund University (LU 85-2004; LU 2011-412).

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**Data availability statement**
Data are available upon reasonable request.

**Author note**
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**Supplemental material**
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