Reduced forced expiratory volume is associated with increased incidence of atrial fibrillation: the Malmö Preventive Project

Linda S.B. Johnson*, Tord Juhlin, Gunnar Engström, and Peter M. Nilsson

Department of Clinical Sciences, Lund University, Skåne University Hospital, Inga-Marie Nilssons väg 49, S-20502 Malmö, Sweden

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Aims

Reduced forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) have been associated with increased incidence of cardiovascular diseases. However, whether reduced lung function is also a risk factor for incidence of atrial fibrillation (AF) is still unclear. We aimed to determine whether lung function predicted AF in the Malmö Preventive Project, a large population-based cohort with a long follow-up.

Methods and results

The study population consisted of 7674 women and 21,070 men, mean age 44.6 years. The cohort was followed on average for 24.8 years, during which time 2669 patients were hospitalized due to AF. The incidence of AF in relationship to quartiles of FEV₁ and FVC and per litre decrease at baseline was determined using a Cox proportional hazards model adjusted for age, height, weight, current smoking status, systolic blood pressure, erythrocyte sedimentation rate, and fasting blood glucose. Forced expiratory volume in one second was inversely related to incidence of AF (per litre reduction in FEV₁) hazard ratio (HR): 1.39 [95% confidence interval (CI): 1.16–1.68; \( P = 0.001 \)] for women, and HR: 1.20 (95% CI: 1.13–1.29; \( P < 0.0001 \)) for men. Forced vital capacity was also inversely related to incidence of AF (per litre reduction in FVC) HR: 1.20 (95% CI: 1.03–1.41; \( P = 0.020 \)) for women, and HR: 1.08 (95% CI: 1.02–1.14; \( P = 0.01 \)) for men. This relationship was consistent in non-smokers as well as smokers, and among individuals younger than the median age of 45.8 years or normotensive subjects.

Conclusion

Impaired lung function is an independent predictor of AF. This may explain some risk of AF that is currently unaccounted for.

Keywords

Atrial fibrillation • Glucose • Hypertension • Lung function • Population • Spirometry

Introduction

Atrial fibrillation (AF) is a rare condition in young age groups, but increases dramatically with age. The prevalence of AF has been estimated to be around 5% at 70 years of age and over 10% among octogenarians.¹ It leads to an increase in mortality independent of associated cardiovascular disease (CVD) of between 50 and 90%.² Known and well-documented risk factors for AF include age, male gender, hypertension, diabetes, and cardiac disease.³ The population attributable fraction of known risk factors has been estimated to be around 50%,³–⁵ which indicates that there may exist additional risk factors for AF that are not fully described and calls for further studies have been made.⁶ Reduced forced expiratory volume in one second (FEV₁) or forced vital capacity (FVC) has repeatedly been associated with increased incidence of CVD.⁷–⁹ This relationship has remained significant after extensive adjustments for cardiovascular risk factors, and low FEV₁ has been documented as a cardiovascular risk factor even in studies of life-long never smokers.¹⁰,¹¹ Previous studies have mainly studied the incidence of myocardial infarction and ischaemic stroke and few have studied whether low FEV₁ or FVC is associated with other CVD outcomes. The Copenhagen Heart Study reported that the incidence of AF was increased for subjects with FEV₁% predicted...
Lung volumes predict incident atrial fibrillation.

This is independent of cardiovascular disease and multiple co-variates.

Method

Study population

The MPP was created in 1974 at the Department of Preventive Medicine at the University Hospital in Malmö, and has been described elsewhere in full detail. A total of 22,444 men and 10,902 women participated in screening activities between the years 1974 and 1992, with an attendance rate over 70%. The aim was to screen a large proportion of the population and to offer preventive intervention to high-risk individuals. Middle-aged men and women born in pre-specified years were invited to participate. The health screening included physical examination, blood sampling, spirometry, and a self-administered questionnaire. Interventions (lifestyle modification, drug therapy) were offered to nearly 25% of screened individuals, but there was no significant effect on CVD mortality and on overall morbidity. Men were mostly screened during 1974–82, and women mostly during 1982–92, resulting in different lengths of follow-up.

The study population for the present study is derived from the MPP. All individuals with prevalent AF were excluded (n = 44). Also excluded were individuals with missing data for FVC (n = 4376), systolic blood pressure (SBP, n = 20), height or weight (n = 3), and current smoking status (n = 13). Individuals with erythrocyte sedimentation rate (ESR) over 50 mm per hour (n = 146) were excluded as this may indicate current pulmonary or airway infection. The study finally included 7674 women and 21,070 men.

Data collection

Height (m) was measured using a fixed stadiometer; weight (kg) was measured in light indoor clothing using a balance beam scale. Blood pressure (mmHg) was measured twice after 10 min of supine rest, using a sphygmomanometer with a modifiable cuff. Blood samples were drawn after overnight fast and analysed using routine methods at the Department of Clinical Chemistry, Malmö University Hospital. Individuals who reported that they were currently smoking were classified as smokers. Sedentary life-style was assessed as positive answer to the question ‘Are you mostly sedentary in your spare time?’; alcohol risk use was assessed as two or more positive answers to the Malmö modification of the Michigan Alcohol Screening Test and low socioeconomic status defined as Statistics Sweden socioeconomic index (SEI) group 11–36.

A screening spirometry was performed by specially trained nurses using a Spirotron apparatus (Drägerwerk AG) with the individual standing without a nose clip; this has been described in more detail elsewhere. One acceptable manoeuvre was required.

National registries

Endpoints were retrieved through linkage with the Swedish Hospital Discharge Register, which is administered by The Swedish National Board of Health and Welfare. A recent validation study showed that the diagnosis of AF or atrial flutter had very high case validity in this register. Participants were followed until first episode of AF (diagnosis codes 427.3 for the 9th revision of International Classification of Diseases, ICD-9, and I48 for the 10th revision, ICD-10), or until censoring by death or emigration from Sweden. Follow-up ended at 30 June 2009. Atrial fibrillation and atrial flutter have not been distinguished due to the similarities of these diagnoses. The study complied with the declaration of Helsinki and has been approved by the regional ethics review board (Dnr. 85/2004).

Statistics

All analyses were performed using IBM SPSS for Windows version 20. Variables with a positively skewed distribution (i.e. fasting blood glucose and ESR) were log-transformed. Forced expiratory volume in one second and FVC were analysed in quartiles and as continuous variables per litre, using Cox regression analysis, stratified on gender. Two statistical models were fitted: Model 1, adjusted for age and height, and Model 2, adjusted for age, height, weight, SBP, ESR, current smoking status, and fasting blood glucose. Data were re-analysed after further stratification by current smoking status. The proportionality assumption of Cox regression was checked visually using Kaplan–Meier plots. A two-sided P < 0.05 was considered significant.

Results

Baseline characteristics

Patients were followed for a mean of 24.8 years (women 24.3 years, men 25.8 years). During this time there were 2669 new cases of AF (518 women and 2151 men). On average, women who received an AF diagnosis did so after 20.1 years of follow-up, and men after 22.3 years. Mean age ± standard deviation (SD) at baseline was 47.7 ± 7.8 for women and 43.5 ± 6.7 for men. Forty-five percent of women and 49% of men were current smokers. Mean systolic blood pressure was 123 mmHg for women and 127 mmHg for men. Baseline characteristics by quartiles of FEV1 are reported in Table 1.

Lung volumes at baseline and incidence of atrial fibrillation

As shown in Table 2, subjects in the lowest quartile of FEV1 had a higher risk of AF compared with subjects in the top quartile for both genders after adjustment for age and height. Model 1, as well as after further adjustment for SBP, current smoking status, weight,
ESR, and fasting glucose, Model 2. The same trend was found when FEV1 was used as a continuous variable (per litre FEV1) (Table 2).

Table 3 presents the relationship between FVC and risk of AF. Men in the lowest quartile of FVC had a higher risk of AF in both models, as well as per litre decrease. For women the risk of AF was lower per litre decrease of FVC for both models. Women in the lowest quartile of FVC had a statistically significant higher risk of AF in Model 1 but not in Model 2.

Analysis was also performed following further stratification by current smoking status to examine the effect of smoking status on the relationship between lung function and risk of incident AF and the results are presented in Table 4. There was a statistically significant increase in risk of AF per litre decrease in FEV1 for smokers and non-smokers of both genders, and a significantly increased risk per litre decrease in FVC for male smokers, and female non-smokers. For male non-smokers and female smokers this trend did not reach statistical significance.

The same analysis was performed after excluding cases of previous myocardial infarction (n = 111) and heart failure (n = 5) at baseline, without any substantial difference in results.

Furthermore, we analysed a subgroup of individuals at or younger than the median age of 45.8 years. The resulting mean age (± SD) was 37.8 ± 5.3 (range: 15.2) for women and 39.2 ± 4.7 (range: 19.3) for men. Hazard ratios (HRs) per litre decrease were consistently

<p>| Table 1 Co-variates by quartile of FEV1 and stratified by gender |
|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Gender</th>
<th>Co-variate</th>
<th>FEV1 quartile 1</th>
<th>FEV1 quartile 2</th>
<th>FEV1 quartile 3</th>
<th>FEV1 quartile 4</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n = 7674)</td>
<td>FEV1 (L) range</td>
<td>0.7–2.2</td>
<td>2.3–2.6</td>
<td>2.7–2.9</td>
<td>3.0–8.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current smoking</td>
<td>65.7</td>
<td>46.9</td>
<td>37.7</td>
<td>32.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Age, years</td>
<td>51.8 (5.6)</td>
<td>49.1 (7.1)</td>
<td>46.3 (7.9)</td>
<td>43.8 (8.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Weight, kg</td>
<td>63.9 (12.4)</td>
<td>64.3 (11.4)</td>
<td>63.9 (10.4)</td>
<td>64.7 (10.1)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Height, cm</td>
<td>160.9 (6.0)</td>
<td>162.6 (5.5)</td>
<td>164.4 (5.4)</td>
<td>167.5 (5.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Fasting blood glucose, mmol/L</td>
<td>4.9 (1.1)</td>
<td>4.9 (1.0)</td>
<td>4.8 (0.7)</td>
<td>4.7 (0.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure, mmHg</td>
<td>126 (18)</td>
<td>124 (17)</td>
<td>122 (15)</td>
<td>120 (14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>ESR, mm/h</td>
<td>11 (7)</td>
<td>10 (7)</td>
<td>9 (6)</td>
<td>8 (6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men (n = 21 070)</td>
<td>FEV1 (L) range</td>
<td>0.4–3.0</td>
<td>3.1–3.5</td>
<td>3.6–4.0</td>
<td>4.1–8.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current smoking</td>
<td>62.1</td>
<td>50.9</td>
<td>44.1</td>
<td>37.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Age, years</td>
<td>46.9 (6.5)</td>
<td>44.2 (6.1)</td>
<td>42.3 (6.1)</td>
<td>40.1 (6.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Weight, kg</td>
<td>75.9 (12.3)</td>
<td>76.7 (11.6)</td>
<td>77.9 (11.0)</td>
<td>79.0 (10.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Height, cm</td>
<td>173.6 (6.4)</td>
<td>176.0 (6.1)</td>
<td>178.0 (5.9)</td>
<td>181.2 (6.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Fasting blood glucose, mmol/L</td>
<td>5.1 (1.1)</td>
<td>5.0 (0.9)</td>
<td>5.0 (0.9)</td>
<td>5.0 (0.9)</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure, mmHg</td>
<td>129 (17)</td>
<td>127 (15)</td>
<td>126 (14)</td>
<td>125 (13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>ESR, mm/h</td>
<td>7 (6)</td>
<td>6 (5)</td>
<td>5 (4)</td>
<td>5 (4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation) unless otherwise stated; P values are for trend across quartiles analysed with analysis of variance for continuous variables and logistic regression for binary variables.

| Table 2 FEV1 and incidence of AF by gender |
|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| FEV1 quartile     | Model 1a        |         |         | Model 2b        |         |         |
|                   | HR  | 95% CI | P value | HR  | 95% CI | P value |
| Women             |     |        |         |     |        |         |
| 1                 | 1.71 | 1.30–2.26 | <0.0001 | 1.40 | 1.05–1.86 | 0.02 |
| 2                 | 1.21 | 0.93–1.59 | 0.16 | 1.05 | 0.79–1.38 | 0.75 |
| 3                 | 1.12 | 0.85–1.48 | 0.42 | 1.06 | 0.80–1.40 | 0.67 |
| 4c                | 1   |         |       | 1   |         |       |
| per litre         | 1.61 | 1.34–1.92 | <0.0001 | 1.39 | 1.16–1.68 | 0.001 |
| Men               |     |        |         |     |        |         |
| 1                 | 1.49 | 1.30–1.72 | <0.0001 | 1.28 | 1.11–1.48 | 0.001 |
| 2                 | 1.23 | 1.08–1.41 | 0.002 | 1.13 | 0.98–1.29 | 0.08 |
| 3                 | 1.07 | 0.93–1.22 | 0.35 | 1.00 | 0.88–1.15 | 0.95 |
| 4d                | 1   |         |       | 1   |         |       |
| per litre         | 1.29 | 1.21–1.38 | <0.0001 | 1.20 | 1.13–1.29 | <0.0001 |

Describes the relationship between FEV1 at baseline and incidence of AF stratified by gender.
aAdjusted for age and height.
bAdjusted for age, height, weight, current smoking status, ESR, fasting blood glucose, and systolic blood pressure. Based on 7626 individuals and 516 cases for women and 20 965 individuals and 2142 cases for men.
cReference category.
dReference category.
positive, and significant for FEV1 for men HR: 1.13 (95% confidence interval (CI): 1.01–1.27; \( P = 0.028 \)) and of borderline significance for women HR: 1.78 (95% CI: 0.99–3.2; \( P = 0.054 \)), after adjustment for Model 2 co-variates.

To test whether the effect of lung volumes on risk of incident AF were related to airway obstruction, we tested quartiles of FEV1/FVC. Individuals in the lowest quartile had a higher risk of AF, for women HR: 1.44 (95% CI: 1.11–1.87; \( P = 0.007 \)) and for men HR: 1.25 (95% CI: 1.11–1.42; \( P < 0.0001 \)) compared with the top quartile, after adjustment for Model 2 co-variates.

To rule out residual confounding by lifestyle factors, we tested a model that included sedentary lifestyle, alcohol risk use, and low socioeconomic status. Inclusion of these variables did not substantially alter results, and they were judged not to be confounding factors of the relationship between lung volumes and incident AF and left out of the final model.

Since coronary heart disease is a known risk factor for AF that could possibly be part of the causal pathway between reduced lung volumes and AF, we tested a model where individuals with incident coronary event during follow-up were censored at the time of the event, resulting in a model where only individuals without coronary heart disease contribute follow-up time. There was no marked difference in results.

Not all women were offered spirometry as part of screening after 1985. To determine whether the missing data had an effect on the relationship between lung volumes and risk of incident AF, a subgroup of women screened before 1986 was analysed, without a substantial difference in results; per litre reduction in FEV1 HR: 1.38 (95% CI: 1.13–1.69, \( P = 0.002 \)). Mean values of co-variates by screening status are reported in Table 5.

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### Table 3  Forced vital capacity and incidence of AF by gender

<table>
<thead>
<tr>
<th>FVC quartile</th>
<th>Model 1a</th>
<th></th>
<th>Model 2b</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>( P ) value</td>
<td>HR</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.50</td>
<td>1.14–1.98</td>
<td>0.004</td>
<td>1.19</td>
</tr>
<tr>
<td>2</td>
<td>1.07</td>
<td>0.82–1.41</td>
<td>0.61</td>
<td>0.92</td>
</tr>
<tr>
<td>3</td>
<td>1.14</td>
<td>0.88–1.47</td>
<td>0.32</td>
<td>1.05</td>
</tr>
<tr>
<td>4c per litre</td>
<td>1.36</td>
<td>1.17–1.59</td>
<td>&lt;0.0001</td>
<td>1.20</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.40</td>
<td>1.22–1.61</td>
<td>&lt;0.0001</td>
<td>1.19</td>
</tr>
<tr>
<td>2</td>
<td>1.08</td>
<td>0.94–1.23</td>
<td>0.26</td>
<td>0.98</td>
</tr>
<tr>
<td>3</td>
<td>1.06</td>
<td>0.93–1.20</td>
<td>0.42</td>
<td>1.01</td>
</tr>
<tr>
<td>4c per litre</td>
<td>1.16</td>
<td>1.09–1.22</td>
<td>&lt;0.0001</td>
<td>1.08</td>
</tr>
</tbody>
</table>

Describes the relationship between FVC and incidence of AF, stratified by gender.

aAdjusted for age and height.

bAdjusted for age, height, weight, current smoking status, ESR, fasting blood glucose, and systolic blood pressure. Based on 7664 individuals and 518 cases for women and 21 063 individuals and 2151 cases for men.

cReference category.

dReference category.

### Table 4  Lung volumes and incidence of AF by gender and smoking status

<table>
<thead>
<tr>
<th>FVC</th>
<th>Smoking Status</th>
<th>Model 1a</th>
<th></th>
<th>Model 2b</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (per 1 L)</td>
<td>95% CI</td>
<td>( P ) value</td>
<td>HR (per 1 L)</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>1.18</td>
<td>0.95–1.48</td>
<td>0.14</td>
<td>1.10</td>
<td>0.88–1.39</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>1.44</td>
<td>1.16–1.77</td>
<td>0.001</td>
<td>1.31</td>
<td>1.05–1.62</td>
</tr>
<tr>
<td>Smokers</td>
<td>1.13</td>
<td>1.04–1.23</td>
<td>0.003</td>
<td>1.07</td>
<td>0.99–1.16</td>
</tr>
<tr>
<td>FEV1</td>
<td>Smokers</td>
<td>1.41</td>
<td>1.08–1.83</td>
<td>0.01</td>
<td>1.33</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>1.64</td>
<td>1.27–2.12</td>
<td>&lt;0.0001</td>
<td>1.45</td>
<td>1.13–1.88</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>1.28</td>
<td>1.17–1.41</td>
<td>&lt;0.0001</td>
<td>1.24</td>
<td>1.12–1.36</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>1.25</td>
<td>1.13–1.37</td>
<td>&lt;0.0001</td>
<td>1.18</td>
<td>1.07–1.30</td>
</tr>
</tbody>
</table>

aAdjusted for age and height.

bAdjusted for age, height, weight, current smoking status, ESR, fasting blood glucose, and systolic blood pressure.

Forced expiratory volume in one second models are based on 4161 individuals and 275 cases for female non-smokers, 3436 individuals and 241 cases for female smokers, 10 720 individuals and 1096 cases for male non-smokers, and 10 323 individuals and 1051 cases for male smokers.
Discussion

Lung function and incidence of atrial fibrillation

The present large population-based cohort study found impaired lung function to be an independent risk factor for AF, after adjustment for age, weight, height, systolic blood pressure, and chronic inflammation as measured by ESR. This was true in both genders, in terms of FEV1 per litre reduction or the risk conferred by being in the lowest quartile of FEV1 (Table 2). Incidence of AF was also related to per litre reduction in FVC in both genders, and to the lowest quartile of FVC in men. For women in the lowest quartile of FVC the trend did not reach statistical significance (Table 3).

Known risk factors for AF include age, male gender, blood pressure, obesity, diabetes, prevalent myocardial infarction, congestive heart failure, and valvular heart disease. We have adjusted for blood pressure, age, gender, weight, inflammation in terms of elevated ESR, and smoking. Independent of these factors lung volumes in terms of FEV1 and FVC predict incident AF in the present study. Excluding patients with a history of myocardial infarction or with prevalent heart failure did not substantially alter results, which further suggests that lung function is an independent risk factor for AF.

To our knowledge this is the largest study so far to have described this relationship. Previously in the Copenhagen City Heart study, the adjusted risk of hospitalization with a main diagnosis of AF increased for subjects with FEV1% predicted <60%. The present study has the advantages of being larger, having a long follow-up of a younger population, and controlling for inflammation as measured by the marker ESR. In the Cardiovascular Health Study, older adults had a HR of 0.75 per litre increase in FEV1. Findings in the present study thus corroborate previous cohort material, and we can conclude that there is strong evidence that impaired lung function independently predicts AF.

Possible causal mechanisms

The MPP cohort is composed of roughly equal proportions of smokers and non-smokers, making it well suited for a stratified analysis. According to this analysis, reduced FEV1 was associated with an increased risk of AF in both smoking and non-smoking men and women. Reduced FVC was also associated with increased risk of AF in smoking men and non-smoking women (Table 4). This suggests that the effect of lung function on risk of AF acts independently of smoking.

We attempted to rule out any confounding by prevalent subclinical heart failure on the relationship between lung volumes and risk of incident AF by analysing the subgroup below the median age of 45.8. Mean age in this group was 38 years in women and 39 years in men. Forced expiratory volume in one second was still significantly associated with incident AF among men in this subgroup, and borderline significant among women. We find that this strengthens the argument that reduced lung volumes confer risk of AF independently of prevalent heart failure, since this condition is rare in that age group. Furthermore, the fact that mean induction time between baseline and AF diagnosis was over 20 years contradicts any hypothesis that reduced lung function is an effect of a primary heart condition with an elevated pressure in the left atria and pulmonary vasculature.

Reduced lung function has been associated with hypertension and it has been shown that the CVD risk is substantially increased if low FEV1 is combined with raised blood pressures. With the purpose of evaluating whether the relationship between a decrease in lung volumes and AF was explained by comorbid hypertension, we fitted the same models in a subgroup of individuals with systolic and diastolic BP below 140/90 mmHg. In these normotensive subjects, we found the same inverse association per litre decrease in FEV1 and risk of AF in both models. The association per litre decrease in FVC and AF was statistically significant for Model 1, but not Model 2. The results in this subgroup imply that reduced lung volumes have an

Table 5 Co-variates by spirometry screening status

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screened</td>
<td>Not screened</td>
<td>P value</td>
<td>Screened</td>
<td>Not screened</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Number of individuals</td>
<td>21 070</td>
<td>1214</td>
<td></td>
<td></td>
<td>7674</td>
<td>2464</td>
<td></td>
</tr>
<tr>
<td>Cases of AF, n (%)</td>
<td>2151 (10.2)</td>
<td>177 (14.6)</td>
<td>&lt;0.0001</td>
<td>518 (6.8)</td>
<td>185 (7.5)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Average time to event, years</td>
<td>25.8 (7.1)</td>
<td>26.3 (8.7)</td>
<td>&lt;0.0001</td>
<td>24.3 (6.2)</td>
<td>19.8 (4.4)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>43.5 (6.7)</td>
<td>48.0 (2.9)</td>
<td>&lt;0.0001</td>
<td>47.7 (7.8)</td>
<td>54.7 (2.5)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>127 (15)</td>
<td>130 (17)</td>
<td>&lt;0.0001</td>
<td>123 (16)</td>
<td>129 (17)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.3 (11.5)</td>
<td>77.8 (11.6)</td>
<td>0.72</td>
<td>64.2 (11.1)</td>
<td>68.4 (12.3)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>177.1 (6.8)</td>
<td>176.3 (6.9)</td>
<td>&lt;0.0001</td>
<td>163.9 (6.1)</td>
<td>163.3 (6.1)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/L</td>
<td>5.0 (1.0)</td>
<td>4.5 (1.0)</td>
<td>&lt;0.0001</td>
<td>4.8 (0.9)</td>
<td>5.1 (1.1)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/l</td>
<td>5 (5)</td>
<td>8 (7)</td>
<td>&lt;0.0001</td>
<td>9 (7)</td>
<td>10 (7)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>49.1</td>
<td>51.4</td>
<td>0.12</td>
<td>45.5</td>
<td>11.0</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Low SEI grade, %</td>
<td>54.5</td>
<td>51.1</td>
<td>0.02</td>
<td>69.8</td>
<td>71.9</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Alcohol risk use (≥2 yes), %</td>
<td>35.7</td>
<td>25.7</td>
<td>0.003</td>
<td>10.3</td>
<td>8.1</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Sedentary life-style, %</td>
<td>54.9</td>
<td>57.8</td>
<td>0.05</td>
<td>55.6</td>
<td>70.0</td>
<td>0.20</td>
<td></td>
</tr>
</tbody>
</table>

Describes co-variates based on whether spirometry was part of the screening in the MPP cohort or not. P values were derived using independent samples t-test for normally distributed continuous variables, Mann–Whitney U test for continuous variables that were not normally distributed (fasting blood glucose and ESR), and Pearson’s χ² test for dichotomous variables.
effect on the risk of AF, that is, at least partly independent of hyper-
tension.

It has been suggested that COPD could cause AF through an in-
flammatory pathway, perhaps through systemic spill-over of inflam-
atory biomarkers through the pulmonary vein to the right atrium.21 We have controlled for ESR and find that reduced lung
volumes confer an increased risk of AF independently of this
marker of systemic inflammation.

Furthermore, it has been suggested that lung function could induce
AF through hypoxia, which has been proposed to act both through
induction of sympathetic drive,21 abnormal automaticity,22 or
through hypercapnia that induces electrophysiological changes.23
However, the risk of AF increased gradually over the range of FEV1
and was not limited to subjects with very low values. Given the rela-
tively low mean age of this cohort and the fact that an effect of lung
volumes on the risk of AF can also be found among non-smokers
(Table 4), it seems that this hypothesis cannot explain our results.
The same argument applies to pulmonary arterial hypertension,
another suggested candidate for explaining how lung volumes can
cause AF.21

Another hypothesis can be found in relation to blood pressure
variability (BPV), a known risk factor for cardiovascular events.24 Re-
cently, it was reported that high-frequency systolic BPV was higher in
subjects with low FEV1.25 Increased BPV is associated with left ven-
tricular hypertrophy,26,27 an echocardiographic predictor of AF.28
From these findings it can be speculated that reduced lung volumes
may increase risk of AF through increased BPV.

Consistently, through analysis of different subgroups, FEV1 was signif-
ificantly associated with risk of AF, suggesting that airway obstruc-
tion may be an important factor linking lung volumes and risk of
incident AF. We tested this theory with analysis of FEV1/FVC,
which was significantly associated with incidence AF. This implies
that airway obstruction may be a mechanism linking reduced lung
volumes and risk of AF.

Beta-agonist inhalations were not in widespread use at the time of
screening and we have no information on whether any individuals in
the study used them at that time or during follow-up. Inhaled
beta-agonists have been proposed to be a risk factor for AF.29
Mechanisms by which AF may be induced include increased heart
rate and decreased potassium concentration.30 However, a recent
risk benefit analysis of long-acting beta-agonists in COPD did not
conclude that there is evidence that these drugs cause an increased
risk of AF.31 and a recent randomized controlled trial did not show
a relationship between use of long-acting beta-agonists and incident
AF.23 The present study showed an increased risk of incident AF along
the full spectrum of lung volumes, whereas it can reasonably be
assumed that bronchodilators were used mostly among individuals
with the worst lung function. In view of this, we believe that use
of beta-agonists is an unlikely explanation for the observed relationship
between lung function and incident AF.

Given the long follow-up time of this cohort, it is a possibility that
reduced lung volumes could lead to an increase in coronary heart
disease, which could then be the cause of the increased risk of AF.
We tested this by re-analysing data after censoring individuals with
a coronary event during follow-up at the time of the event. This did
not markedly change results. In view of this, one can assume that
the causal pathway between reduced lung volumes and AF is
probably not through induction of coronary heart disease. A more
probable pathway is through slight haemodynamic changes. Lung
volumes could affect intrathoracic pressure, and thereby influence
venous return and BPV, perhaps due to changes in both breathing fre-
quency and volume. Over time such factors could possibly lead to
changes in volume and pressure load on the heart, with resultant fi-
brosis and dilation of the heart chambers that can act as substrate
for AF.

Strengths and limitations

Strengths of this study include its high participation rate, large size,
and long follow-up. Furthermore, Swedish National Hospital
Discharge Records are of high quality and have been shown to be
valid for the diagnosis of AF.3 We have controlled for many documen-
ted risk factors for AF, and ruled out other potential confounders.
Any residual confounding can be assumed to be small.

We cannot rule out that lung function could influence some other
factor that later acts to cause AF. Low FEV1 has been associated with
increased incidence of hypertension and diabetes.33,34 Even though
we have adjusted for blood pressure and diabetes at baseline, these
risk factors as well as other diseases we have not controlled for such
as thyroid disease and valvular heart disease, could still represent
a link between FEV1 and AF. If so, reduced FEV1 would be an early
marker of increased AF risk. Nor can we rule out that, e.g. developmen-
tal factors in early life could be common determinants of lung function
as well as risk of AF. Regardless, the fact that a low FEV1 or FVC in a
clinical setting indicates an increased risk of developing AF is useful clin-
ically and for the development of risk prediction models.

Cases with AF were retrieved from the Swedish Hospital discharge
register. A recent validation study showed that case validity of this
diagnosis is very high.5 This register has been operating in the south
of Sweden during the entire follow-up period and became nation-
wide in 1987. However, many AF patients are treated as outpatients
without hospitalization and these cases have been missed. Prevalent
cases were retrieved from the same database. We cannot rule out
that some individuals with subclinical and undetected AF could
have been included in the study; however, given the low mean age
of the cohort this number can be assumed to be small.

The spirometries were performed at the baseline screening exam-
novation before the current guidelines for measurements of lung func-
tion were published.18 The lung function measurements did not meet
the current standards, e.g. only one acceptable manoeuvre was
required. However, if anything, poor precision of the measurements
should reduce the relationship with the incidence of AF.

Not all women screened after 1985 were offered spirometry as part
of the examinations. This is a limitation. We addressed this
issue by analysing a subgroup of individuals screened before 1986,
wherein results were similar. Furthermore, the relationship
between lung function and incident AF was seen in men as well as
in women. We find, therefore, that this limitation appears not to
have influenced results.

High doses of systemic corticosteroids, but not low-intermediate
doses or inhaled corticosteroids, have been shown to increase the
risk of AF.15 We have no data regarding medication use during follow-
up, and thus cannot rule out that use of corticosteroids during follow-
up could have influenced results. However, we do not believe such
use to be common enough to have a substantial effect on results.
It is also likely that other risk factors, such as smoking habits, have changed during the long follow-up period of 25 years. Prevalence of smoking has decreased dramatically in Sweden during this time period. Since smoking was substantially more common in subjects with low FEV₁, it can be assumed that this group gained most from smoking cessation. If anything, this would reduce the relationship between FEV₁ and AF and bias the results towards null.

Conclusion

An independent and inverse relationship exists between FEV₁ and AF and bias the results towards null. It is also likely that other risk factors, such as smoking habits, have changed during the long follow-up period of 25 years. Prevalence of smoking has decreased dramatically in Sweden during this time period. Since smoking was substantially more common in subjects with low FEV₁, it can be assumed that this group gained most from smoking cessation. If anything, this would reduce the relationship between FEV₁ and AF and bias the results towards null.

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Conflict of interest

none declared.

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References


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