CLINICAL RESEARCH

Pulmonary dysfunction and development of different cardiovascular outcomes in the general population

Le dysfonctionnement pulmonaire et le développement de différentes maladies cardiovasculaires dans la population générale

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Summary
Background. — Pulmonary dysfunction and cardiovascular disease are major causes of impaired health status in later life, and co-development of these diseases has been reported.
Aim. — To better understand the pathobiology involved in the co-development of these diseases.
Methods. — We investigated the impact of pulmonary dysfunction on the development of cardiovascular disease among people aged ≥ 50 years in the English longitudinal study of ageing (ELSA). Hazard ratios were estimated by Cox proportional hazards regression models, with and without a time-dependent update of exposure and confounders. Pulmonary function was divided into three categories, with the least affected category as the reference.

Abbreviations: CI, Confidence interval; CVD, Cardiovascular disease; COPD, Chronic obstructive pulmonary disease; ELSA, English longitudinal study of ageing; FEV1, Forced expiratory volume; FVC, Forced vital capacity; HR, Hazard ratio; PD, Pulmonary dysfunction.
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Results. — People with pulmonary dysfunction were at higher risk of developing cardiovascular disease than those with normal pulmonary function: the hazard ratio for pulmonary dysfunction versus healthy in the time-dependent crude analysis of model 1, adjusted for age, body mass index, sex, angina pectoris and heart arrhythmia, was 1.49 (95% confidence interval 1.2—1.9). The effect varied with the precise definition of pulmonary dysfunction and the subtype of the cardiovascular disease, and decreased after correction for some additional confounders but not after correction for inflammatory biomarkers.

Conclusions. — A history of pulmonary disease increased the risk of developing cardiovascular disease, but inflammation did not seem to alter the effect of pulmonary dysfunction on cardiovascular disease development. This insight may lead to better understanding and treatment of cardiovascular comorbidities in pulmonary disease; it also indicates that the potentially beneficial effect of targeted anti-inflammatory drugs for pulmonary disease, in terms of reducing cardiovascular risk in these patients, may be limited.

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MOTS CLÉS
Épidémiologie ; Accident vasculaire cérébral ; Insuffisance cardiaque ; Infarctus du myocarde aigu ; Marqueurs inflammatoires

Résumé

Contexte. — Le dysfonctionnement pulmonaire et les maladies cardiovasculaires sont des causes majeures de la dégradation de l’état de santé au troisième âge.

Objectif. — Nous avons voulu étudier l’impact du dysfonctionnement pulmonaire sur le développement de maladies cardiovasculaires.

Méthodes. — Sur la base des données des participants à l’étude « English longitudinal study of ageing », nous avons estimé les hazard-ratios grâce à des modèles de régression de Cox avec et sans mise à jour temporelle des facteurs d’exposition et de confusion. La fonction pulmonaire a été établie en trois catégories, la moins touchée servant de référence.

Résultats. — Les personnes présentant un dysfonctionnement pulmonaire avaient plus de risque de développer une maladie cardiovasculaire que les personnes avec une fonction pulmonaire normale (hazard-ratios pour le dysfonctionnement pulmonaire vs. sain selon l’analyse temporellement mise à jour du modèle 1 ajusté pour l’âge, l’IMC, le sexe, l’angine de poitrine et l’arythmie cardiaque était de 1,49 [IC 95 % 1,2—1,9]). L’effet variait selon la définition précise du dysfonctionnement pulmonaire ainsi que selon le sous-type de la maladie cardiovasculaire et diminuait après ajustement pour certains facteurs de confusion supplémentaires, mais pas après ajustement pour des biomarqueurs inflammatoires.

Conclusions. — L’incidence d’une maladie pulmonaire antérieure augmentait le risque de développer une maladie cardiovasculaire, mais l’inflammation ne semblait pas altérer l’effet du dysfonctionnement pulmonaire sur le développement de maladies cardiovasculaires. Ce gain de connaissance pourrait amener à une meilleure compréhension et donc un meilleur traitement des comorbidités vasculaires des maladies pulmonaires. Cela indique également que l’effet potentiellement bénéfique des anti-inflammatoires ciblant les conditions pulmonaires pourrait être limité quant à la réduction du risque cardiovasculaire.

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Background

Cardiovascular disease (CVD) and pulmonary dysfunction (PD) are major contributors to cardiovascular death and mortality in the elderly, with chronic obstructive pulmonary disease (COPD) in particular having a high prevalence of 13.3% in those aged > 35 years in the UK [1]. Important diagnostic criteria for COPD include decrease in forced expiratory volume (FEV1) and in the ratio between FEV1 and the forced vital capacity (FVC) [2,3], while a decrease in both FVC and FEV1 is important for the diagnosis of restrictive pulmonary disease, such as pulmonary fibrosis [4]. Clinically, in the diagnosis of PD, these spirometric data are often used in combination with symptomatic data, such as dyspnoea and phlegm from the chest [2].

COPD and pulmonary fibrosis have been described as being associated with CVD development [5,6]. The relationship between CVD morbidity and mortality has been reported to be stronger in patients with COPD than in the general population [7–10]. Furthermore, in patients with COPD, the severity of airflow limitation was shown to increase the risk of developing CVD [6]. However, an effect between PD and CVD progression may work both ways. Patients with CVD and COPD had an increased risk of

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hospital admission for acute exacerbation of COPD, and patients admitted to hospital for myocardial infarction with concomitant COPD had a higher risk of mortality compared with patients admitted for myocardial infarction without COPD [11,12].

There are further complications because of the large set of shared risk factors, such as smoking, physical inactivity, old age, high body mass index, high blood pressure and inflammation [6,7,13].

Studies investigating whether COPD affects cardiovascular risk through inflammatory processes have been inconsistent [14,15]. Potential biomarkers of these processes in both PD and CVD are fibrinogen, C-reactive protein and ferritin [13,16,17]. An increase in fibrinogen is well known to be associated with a risk of certain types of CVD, and has been reported to be associated with PD [17]. Persistent inflammation, defined by ongoing elevation of blood inflammatory biomarkers, such as C-reactive protein and fibrinogen, is assumed to specifically characterize an inflammatory subphenotype of COPD, which has yet to be fully validated with regard to clinical outcomes [18]. Ferritin has been suggested to be associated with CVD, although its role in PD has yet to be established [19].

Anti-inflammatory medications, such as steroids and several targeted inhibitors of inflammation, have been evaluated (alone and in certain combinations) for the treatment of COPD. So far, these medications have shown a limited effect on COPD in the overall patient population, and sometimes have very relevant side-effects [20]. Yet these drugs might have a potential beneficial effect on CVD risk, as the increased risk of CVD in these patients may be linked to PD-associated inflammation [21]. Therefore, in this study, we aimed to better understand how PD is linked to the manifestation of first CVD events in the general elderly population, with a special interest in the role of inflammatory biomarkers.

Methods

Dataset preparation

The English Longitudinal Study of Ageing (ELSA) is funded by a consortium of UK government departments and the National Institute on Aging in the USA, and is collecting longitudinal multidisciplinary data from a representative sample of the English population aged ≥ 50 years living at a private residential address over a period of 8 waves (waves 0–7). This study included 11,140 people, with detailed data on pulmonary function and confounders collected by trained nurses. Medical information, such as laboratory values (inflammatory biomarkers), blood pressure measurements and lung function data, were collected every 4 years by nurse visits beginning at wave 2, while information on the disease state was collected systematically in the regular follow-up interviews every 2 years from wave 2 onwards.

Definition of exposure

Pulmonary function was divided into three categories (PD1–3), which were based primarily on the proportions of expected FEV1, FEV1/FVC and self-reported PD medication. The sensitivity analysis also included symptoms of dyspnoea and phlegm and the chest (Table 1) [22,23].

Follow-up timing and outcome

The first baseline measurements of lung function and important sources of potential confounding were performed at wave 2. For patients joining the study at later time points or who missed the first lung function measurements at wave 2, baseline measurements were taken at wave 4 and wave 6. Drop out/end of study (censoring) was defined by reaching the endpoint (first CVD event), last date of study participation (last interview date) or death of the subject.

Several first CVD outcome events were studied, including self-reported doctor-diagnosed stroke, myocardial infarction and heart failure. We also studied a combined endpoint, which included the CVD endpoints mentioned previously, as well as CVD-related death. Cases of non-CVD-related death were censored.

Statistical analysis

All analyses, including the crude analysis and the descriptive analysis shown in Table 2, were performed by taking the cross-sectional analytical weights for the nurse visit datasets, as provided by the ELSA study team, into account. People with missing weight or weight < 0.3 were not included in the analysis. We performed Cox proportional hazards regression to adjust to obtain hazard ratios (HRs) and their 95% confidence intervals (CIs). In the main analysis, PD was divided into three categories, with no PD (PD0) as the reference group. Kaplan-Meier graphs were generated to check for distinct violations of the proportional hazards assumption in the progression of the curves (Fig. 1). Baseline measures used to adjust our analysis were body mass index, age, sex, angina pectoris, heart arrhythmia (model 1), plus smoking, sport and blood pressure (model 2) and biomarkers of inflammation (model 3). In the time-dependent Cox regression, all exposure and confounders except sex, age and smoking were considered, with updated levels every 4 years, where possible. In the sensitivity analysis, PD was divided into four categories, again with PD0 as the reference group, and missing data were imputed.

A more detailed description of the methods can be found in the Appendix.

Results

Characteristics

The ELSA dataset included a total of 11,140 sample members, who were also part of the nursing datasets (starting at wave 2) and had nursing dataset weights, together with data on confounders and data needed to establish baseline pulmonary function status. Of these, 688 were excluded because CVD outcome events were reported before exposure, 931 were excluded because of missing data on CVD, 208 were excluded because it was not possible to determine whether a reported event was new or pre-existing, five
Table 1  Status of pulmonary function.

<table>
<thead>
<tr>
<th>Category</th>
<th>Expected FEV1 &lt; 80%</th>
<th>FEV1/FVC &lt; 70%</th>
<th>Medication</th>
<th>Dyspnoea or phlegm from the chest</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD0 (healthy)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>PD1 (intermediate/mild dysfunction)</td>
<td>Positive in at least one of the categories</td>
<td>Positive in at least one of the categories</td>
<td>Yes or no</td>
<td>—</td>
</tr>
<tr>
<td>PD2 (diseased)</td>
<td>Positive in at least two of the categories</td>
<td>Positive in at least two of the categories</td>
<td>Yes (Dyspnoea)</td>
<td>—</td>
</tr>
<tr>
<td>PD3 (severely diseased)</td>
<td>Positive in at least two of the categories and with dyspnoea</td>
<td>Positive in at least two of the categories and with dyspnoea</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

FEV1: forced expiratory volume; FVC: forced vital capacity; PD: pulmonary dysfunction.

were excluded because FEV1/FVC was > 1.1 and 209 were excluded because of missing data on baseline confounding factors in model 1. This left 9099 people available for primary analysis in model 1 (Fig. A.1).

In this dataset, during a total of 61,383 person-years of follow-up (with a median of 78.92 months per person; minimum 0.49, maximum 129.07), 587 people reported a first cardiovascular outcome event, yielding an overall incidence rate of 9.6 per 1000 person-years. Because of additional missing data on confounders (Table A.1), 8260 people with 524 events were available for complete-case analysis in model 2, and 6476 people with 390 events were available for model 3 (Fig. A.1).

The baseline characteristics of the study participants, stratified to the three predefined categories of the exposure PD, are shown in Table 2. As expected, the more-affected subgroups were older, had more previous smokers, higher concentrations of C-reactive protein and more people with a history of angina. Also, the COPD symptoms dyspnoea and phlegm from the chest increased towards the most affected subgroup. In this group, 13.8% had an indication for medication for a lung condition (Table 2).

**PD and CVD outcomes**

The incidence of CVD outcomes was higher in participants with PD versus those without PD (Fig. 1). Overall, the incidence per 1000 person-years for the combined CVD outcomes was 8.0% for those without PD, 11.3% for PD1 and 13.1% for PD2 (Table 3); these data correspond with rate ratios of 1.4 (95% CI 1.2–1.4) for PD1 and 1.7 (95% CI 1.3–2.0) for PD2 (Table 3, Fig. 2). Adjustment for potential confounders (model 1) attenuated these HRs for overall CVD outcomes to 1.25 (95% CI 1.02–1.53) for PD1 and 1.37 (95% CI 1.09–1.71) for PD2. Additional correction in model 2 led to a further decrease in HR to 1.20 (95% CI 0.97–1.48) for PD1 and 1.16 (95% CI 0.90–1.50) for PD2. Finally, additional adjusting for biomarkers indicative of inflammation in model 3 resulted in a slight increase in HRs to 1.32 (95% CI 1.04–1.69) for PD1 and to 1.23 (95% CI 0.92–1.66) for PD2 (Table 3, Fig. 2).

When analysing disease-specific outcomes (i.e. stroke, myocardial infarction and heart failure), results indicated a stronger association for PD2 versus PD0 compared with PD1 versus PD0 for uncorrected rate ratios for stroke and heart failure (Tables A.2–A.4). However, overall associations...
Table 2  Description of baseline characteristics of those included in the analyses**.

<table>
<thead>
<tr>
<th></th>
<th>All subjects (n = 9099)</th>
<th>PD0 (n = 5413)</th>
<th>PD1 (n = 2300)</th>
<th>PD2 (n = 1386)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years); age &gt; 99 years, n = 43 (0.5%)</td>
<td>62 ± 9.7</td>
<td>61 ± 9.4</td>
<td>63 ± 10.0</td>
<td>65 ± 9.8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.1 ± 5.0</td>
<td>28.1 ± 4.8</td>
<td>28.4 ± 5.5</td>
<td>27.4 ± 5.1</td>
</tr>
<tr>
<td>Men</td>
<td>4624</td>
<td>2732 (46.1)</td>
<td>1175 (46.4)</td>
<td>717 (48.2)</td>
</tr>
<tr>
<td>Smoking status (n = 27 missing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>1336</td>
<td>936 (15.9)</td>
<td>297 (11.8)</td>
<td>103 (7.0)</td>
</tr>
<tr>
<td>Not currently smoking</td>
<td>6944</td>
<td>4315 (73.1)</td>
<td>1709 (67.8)</td>
<td>920 (62.0)</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>1627</td>
<td>652 (11.0)</td>
<td>514 (20.4)</td>
<td>461 (31.1)</td>
</tr>
<tr>
<td>Sport (vigorous or moderate sport at least once/week)</td>
<td>3071</td>
<td>2056 (34.7)</td>
<td>693 (27.4)</td>
<td>322 (21.7)</td>
</tr>
<tr>
<td>High blood pressure (n = 812 missing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP &lt; 90 and SBP &lt; 140 mmHg and no medication</td>
<td>5116</td>
<td>3240 (59.3)</td>
<td>1225 (51.1)</td>
<td>651 (50.4)</td>
</tr>
<tr>
<td>DBP ≥ 90 or SBP ≥ 140 mmHg and no medication</td>
<td>1730</td>
<td>1023 (18.7)</td>
<td>445 (19.7)</td>
<td>262 (20.3)</td>
</tr>
<tr>
<td>DBP ≥ 100 or SBP ≥ 160 mmHg or medication</td>
<td>2172</td>
<td>1200 (22.0)</td>
<td>595 (26.3)</td>
<td>378 (29.3)</td>
</tr>
<tr>
<td>History of arrhythmia</td>
<td>613</td>
<td>338 (5.7)</td>
<td>159 (6.3)</td>
<td>116 (7.8)</td>
</tr>
<tr>
<td>History of angina</td>
<td>521</td>
<td>223 (3.8)</td>
<td>177 (7.0)</td>
<td>120 (8.1)</td>
</tr>
<tr>
<td>C-reactive protein (n = 1863 missing)</td>
<td>1.8 [0.8—3.7]</td>
<td>1.6 [0.8—3.2]</td>
<td>2.0 [0.9—4.2]</td>
<td>2.1 [1.0—4.7]</td>
</tr>
<tr>
<td>Fibrinogen (mg/L) (n = 1957 missing)</td>
<td>3.2 (0.7)</td>
<td>3.1 (0.6)</td>
<td>3.2 (0.6)</td>
<td>3.3 (0.7)</td>
</tr>
<tr>
<td>Ferritin (mg/L) (n = 1858 missing)</td>
<td>94.0</td>
<td>96.0 [53.0—160.0]</td>
<td>89.0 [51.0—160.0]</td>
<td>93.0 [55.0—154.6]</td>
</tr>
<tr>
<td>Positive for phlegm from chest</td>
<td>961</td>
<td>365 (6.1)</td>
<td>276 (10.9)</td>
<td>323 (21.7)</td>
</tr>
<tr>
<td>Positive for dyspnoea</td>
<td>1576</td>
<td>624 (10.5)</td>
<td>474 (18.7)</td>
<td>478 (32.2)</td>
</tr>
<tr>
<td>Expected FEV1 &lt; 80%</td>
<td>2861</td>
<td>0</td>
<td>1393 (55)</td>
<td>1468 (98.7)</td>
</tr>
<tr>
<td>FEV1/FVC &lt; 70%</td>
<td>2551</td>
<td>0</td>
<td>1101 (43.5)</td>
<td>1450 (97.5)</td>
</tr>
<tr>
<td>Taking medication for lung condition</td>
<td>241</td>
<td>0</td>
<td>37 (1.4)</td>
<td>205 (13.8)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation, number (%) or median [interquartile range]. DBP: diastolic blood pressure; FEV1: forced expiratory volume; FVC: forced vital capacity; PD: pulmonary dysfunction; SBP: systolic blood pressure.

** Table heads represent observed case numbers; rows depict weighted case numbers; missing data on confounders in models 2 and 3 are included; values in rows represent weighted measures.

Figure 1. Kaplan-Meier failure estimates. People with a diagnosis of pulmonary dysfunction (PD) are more likely to experience a cardiovascular disease event earlier than healthy people. In this analysis, there was no correction for confounding factors. The blue line shows people with no measured decrease in lung function (PD0), the red line shows those with a decline in one of the measured lung function variables or with an indication for medication for pulmonary disease (PD1) and the green line shows those with a decrease in both measured lung function variables (PD2).

in subtype-specific analyses were mostly minor and imprecise when adjusted for the different potential confounders (Tables A.2—A.4).

Time-dependent analyses

We also performed time-dependent Cox regression analysis, as this allowed us to update the data on confounding factors and exposure every 4 years during follow-up. Compared with the analysis without time-dependent updates, these analyses led to stronger associations between PD2 versus PD0 and overall CVD outcome analysis in all regression models, and showed stronger associations of PD2 versus PD0 with stroke, myocardial infarction and heart failure, especially in model 1 (Tables 3 and 4, Figs. 2 and 3, Tables A.2—A.7). The different point estimates decreased in model 2, and unexpectedly increased in model 3, when adjusting for inflammatory biomarkers.

Sensitivity analysis 1: PD definitions

To understand the robustness of these results, we repeated these analyses with a slightly different definition of PD that
Table 3  Impact of pulmonary dysfunction on cardiovascular disease outcome.

<table>
<thead>
<tr>
<th></th>
<th>Overall CVD events (n)</th>
<th>Person-years</th>
<th>Incidence rate per 1000 person-years (%)</th>
<th>Rate ratio (95% CI)</th>
<th>Model 1 (587 cases; 9099 individuals)</th>
<th>Model 2 (524 cases; 8260 individuals)</th>
<th>Model 3 (390 cases; 6476 individuals)</th>
<th>PD sens 2; model 2 (imputed)</th>
<th>PD sens 2; model 3 (imputed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD main model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD0</td>
<td>294</td>
<td>36,858</td>
<td>8.0</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref) 1.17 1.18</td>
</tr>
<tr>
<td>PD1</td>
<td>176</td>
<td>15,498</td>
<td>11.3</td>
<td>1.4 (1.2–1.4)</td>
<td>1.25 (1.02–1.53)</td>
<td>1.20 (0.97–1.48)</td>
<td>1.32 (1.04–1.69)</td>
<td>1.25 (1.02–1.53)</td>
<td>1.20 (0.97–1.48) 1.32 (1.04–1.69)</td>
</tr>
<tr>
<td>PD2</td>
<td>119</td>
<td>9027</td>
<td>13.1</td>
<td>1.7 (1.3–2.0)</td>
<td>1.37 (1.09–1.71)</td>
<td>1.16 (0.90–1.50)</td>
<td>1.23 (0.92–1.66)</td>
<td>1.37 (1.09–1.71)</td>
<td>1.16 (0.90–1.50) 1.23 (0.92–1.66)</td>
</tr>
<tr>
<td>PD sens 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD0</td>
<td>220</td>
<td>31,022</td>
<td>7.10</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref) 1.14 1.14</td>
</tr>
<tr>
<td>PD1</td>
<td>177</td>
<td>17,411</td>
<td>10.16</td>
<td>1.43 (1.18–1.74)</td>
<td>1.20 (0.98–1.48)</td>
<td>1.18 (0.95–1.47)</td>
<td>1.28 (0.99–1.65)</td>
<td>1.20 (0.98–1.48)</td>
<td>1.18 (0.95–1.47) 1.28 (0.99–1.65)</td>
</tr>
<tr>
<td>PD2</td>
<td>144</td>
<td>9939</td>
<td>14.47</td>
<td>2.04 (1.66–2.52)</td>
<td>1.63 (1.36–2.04)</td>
<td>1.53 (1.2–1.95)</td>
<td>1.66 (1.25–2.2)</td>
<td>1.63 (1.36–2.04)</td>
<td>1.53 (1.2–1.95) 1.66 (1.25–2.2)</td>
</tr>
<tr>
<td>PD3</td>
<td>48</td>
<td>3011</td>
<td>15.80</td>
<td>2.25 (1.65–3.07)</td>
<td>1.57 (1.10–2.24)</td>
<td>1.24 (0.84–1.85)</td>
<td>1.35 (0.85–2.14)</td>
<td>1.57 (1.10–2.24)</td>
<td>1.24 (0.84–1.85) 1.35 (0.85–2.14)</td>
</tr>
</tbody>
</table>

Data are expressed as hazard ratio (95% confidence interval [CI]), unless otherwise indicated. CVD: cardiovascular disease; PD: pulmonary dysfunction; ref: reference; sens: sensitivity analysis.
Table 4  Time-dependent analysis: impact of pulmonary dysfunction (PD) on cardiovascular disease outcome.

<table>
<thead>
<tr>
<th></th>
<th>Overall CVD</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>PD sens 2; model 2 (imputed)</th>
<th>PD sens 2; model 3 (imputed)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD main model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD0</td>
<td>294</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>PD1</td>
<td>176</td>
<td>1.25 (1.03–1.53)</td>
<td>1.18 (0.96–1.46)</td>
<td>1.24 (0.97–1.6)</td>
<td>1.17 (0.95–1.42)</td>
<td>1.16 (0.95–1.42)</td>
</tr>
<tr>
<td>PD2</td>
<td>119</td>
<td>1.49 (1.2–1.9)</td>
<td>1.23 (0.96–1.59)</td>
<td>1.32 (0.99–1.76)</td>
<td>1.25 (0.99–1.59)</td>
<td>1.23 (0.97–1.55)</td>
</tr>
<tr>
<td><strong>PD sens 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD0</td>
<td>220</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>PD1</td>
<td>177</td>
<td>1.46 (1.19–1.8)</td>
<td>1.46 (1.18–1.82)</td>
<td>1.5 (1.16–1.94)</td>
<td>1.37 (1.11–1.69)</td>
<td>1.36 (1.11–1.68)</td>
</tr>
<tr>
<td>PD2</td>
<td>144</td>
<td>1.79 (1.43–2.25)</td>
<td>1.62 (1.26–2.08)</td>
<td>1.82 (1.36–2.42)</td>
<td>1.57 (1.24–1.99)</td>
<td>1.55 (1.22–1.94)</td>
</tr>
<tr>
<td>PD3</td>
<td>48</td>
<td>1.84 (1.3–2.6)</td>
<td>1.46 (0.98–2.17)</td>
<td>1.52 (0.95–2.41)</td>
<td>1.52 (1.06–2.17)</td>
<td>1.48 (1.03–2.12)</td>
</tr>
</tbody>
</table>

Data are expressed as hazard ratio (95% confidence interval), unless otherwise indicated. CVD: cardiovascular disease; PD: pulmonary dysfunction; ref: reference; sens: sensitivity analysis.
also included the self-reported PD symptoms of dyspnea and phlegm from the chest for diagnosis. An additional category (PD3) was created, comprising PD2 plus dyspnea, which has been associated with disease severity and cardiac comorbidity [24,25].

When comparing the results of the crude analysis and the sensitivity analysis, HRs for PD2 and PD3 in the overall association with CVD outcomes were moderately higher with the adapted definitions (Table 3, Fig. 2). In the time-dependent approach, however, these updated exposure definitions led to a more pronounced increase in HRs for the association of PD1, PD2 and PD3 with overall CVD outcomes as well as with stroke and heart failure in all three models (Table 4, Fig. 3, Tables A.5 and A.7). Interestingly, myocardial infarction analyses changed only to a limited extent (Table A.6). Higher HRs for PD3 versus PD0 compared with PD1 and PD2 versus PD0 were seen for heart failure and, again to a limited extent, for myocardial infarction, but not for stroke or in the overall analysis (Table 4, Fig. 3, Tables A.5–A.7).

Sensitivity analysis 2: multiple imputation

When missing data where imputed, the results overall did not differ substantially from the complete-case analyses. The decrease in HRs for PD2 versus PD0 when comparing model 1 and model 2 remained, but additional adjustment for biomarkers did not affect the HR any further (HR for model 2 1.18 [95% CI 0.93–1.49] versus HR for model 3 1.15 [95% CI 0.91–1.46]), indicating that the change in HR for model 3 in the complete-case analyses might be driven by a patient selection that is inherent to this analysis approach (Table 3, Fig. 2). Similar results were seen for
the time-dependent and sensitivity analyses (Tables 3 and 4, Figs. 2 and 3, Tables A.2–A.7).

Although the results of the imputation analysis further suggested that there was no effect of inflammatory biomarkers on PD-associated risk of developing CVD outcomes, fibrinogen was found to be independently associated with CVD outcome development in the overall analysis, and ferritin and fibrinogen were both associated with the development of myocardial infarction, even after adjustment for other co-variables in model 3 (data not shown).

Discussion

Especially in the time-dependent analysis, with updated levels of exposure and confounding factors, our study showed associations between PD and CVD events, also after correction for age, sex, body mass index, angina pectoris and heart arrhythmia. Associations decreased after further correction for sport, smoking and hypertension, but remained significant.

Additional correction for inflammatory ferritin, fibrinogen and C-reactive protein markers, in contrast, did not lead to a relevant further decrease in HRs for CVD outcomes in people with PD, suggesting a limited role for inflammation in the association between PD and CVD risk. This may be informative with regard to the ability of anti-inflammatory PD medication to prevent CVD in this population. This study, however, was not designed to answer the clinical question about whether patients with PD would benefit overall from any medication, and no such conclusions are thus warranted.

Several limitations of our study should be considered in the interpretation of these results. First, our study included a representative sample of the English population aged ≥50 years, where—because of the chronic nature of the exposure and confounders—baseline values might underestimate the true relationship. Therefore, we applied a time-dependent analysis, which showed even stronger effect estimates. In this analysis, we applied last observation forward where we had missing data, which can lead to a biased estimate of the treatment effect. Nonetheless, health status in patients with PD should have worsened progressively from the start of the study to the end. Therefore, carrying forward an intermediate value is a conservative estimate of the progression of exposure, as well as the status of variables influencing exposure.

Second, some of data were self-reported by the participants, which can sometimes be inaccurate, and can increase the variance in the dataset. Unfortunately, for the important confounder variable of smoking, detailed information on pack-years was not available. This may result in a bias towards or away from unity. Self-reporting can also lead to under-reporting of clinical events, leading to lower absolute risks, and thus power, in our analyses [26,27].

Third, the applied definition of PD might be imprecise; although we always took the best of three technically-successful values per time point, we cannot exclude a certain level of non-compliance of participants or the presence of non-permanent lung diseases, such as infection, which can bias results towards unity [27]. To address this problem, we added a sensitivity analysis that applied a different definition of PD by additionally including phlegm from the chest and dyspnoea as diagnostic markers for classification of exposure.

Finally, missing baseline confounder data in our analysis of models 2 and 3 led to a reduction in people available for analysis. Interestingly, point estimates tended to increase slightly when biomarkers of inflammation were included in the analyses, which might have been caused by the selection of study participants giving blood samples for biomarker analysis. The additional multiple-imputation analyses, however, still did not suggest that the relationship between PD and CVD was severely affected by inflammatory processes.

Despite the limitations, the large cohort of randomly selected participants used in our study facilitates direct comparison of several risk and disease-modifying factors in different subtypes of CVD, in a representative subset of the elderly English population. Dyspnoea has been associated with disease severity in PD [28], but can also be an independent diagnostic criterion for the cardiac diseases of myocardial infarction and heart failure. In the sensitivity analysis, the definition of PD3 was based on the diagnosis of PD by expected FEV1 and FEV1/FVC ratio plus dyspnoea, while the definition of PD2 included PD diagnosis by decline in one of the lung function variables with dyspnoea, or in both lung function variables without dyspnoea. We saw slightly higher HRs in PD3 versus PD0 compared with PD2 versus PD0 for the cardiac outcomes, but not for the stroke and overall CVD outcomes analyses. A generally increased presence of underlying cardiac comorbidity in PD has recently been supported by a systematic review [29]. Our results indicate that the presence of underlying cardiac comorbidity may also increase with PD severity, causing a higher risk of heart failure and myocardial infarction outcomes, but not stroke, in PD3 versus PD0 compared with PD2 versus PF0 analyses. Whether this is caused, in part, by a reverse causation of stronger decline in pulmonary function in the presence of undiagnosed cardiac disease, or whether it reflects a causal connection between increased PD severity and faster progression of underlying cardiac disease, is unclear.

Conclusions

Generally, Kaplan-Meier analysis, rate ratios and HRs in the main model 1 showed an increased risk of CVD development, especially in PD2 versus PD0 for the overall analysis, as well as stroke and heart failure for the subanalyses. Moreover, independent of the alteration of the effects of PD on CVD outcomes by confounding factors, PD had a small, but measurable, effect on the development of first CVD outcomes that could be seen best in a time-dependent sensitivity analysis for overall CVD outcome events, as well as for stroke, when using dyspnoea and/or phlegm from the chest as additional diagnostic criteria for PD2 and PD1.

Results of our study further suggest that the direct effect that PD has on CVD development cannot be explained by concentrations of inflammatory biomarkers. Although the inflammatory biomarkers were associated with increased CVD risk in our study, adjustment for these variables did not seem to alter the effects of PD on CVD outcomes to a great extent. This suggests that the effect of PD on CVD may not be relevantly influenced by inflammatory processes. With
regard to the potential implications of these results for targeted anti-inflammatory PD medication in the prevention of CVD comorbidities, we did not study the effect of such medication on CVD development in patients with PD directly. Therefore, no direct conclusions on the beneficial effects of anti-inflammatory PD medication can be drawn from these data. However, it will be interesting to see whether or not future studies can show effects of inflammatory PD medication on the manifestation of CVD comorbidities.

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Acknowledgements

The data are publicly available through the UK data archive. ELSA was developed, and data were collected, by a team based at the NatCen social research, University College London and the Institute for fiscal studies.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2017.07.001.

References


