Chronic obstructive pulmonary disease and the risk of 12 cardiovascular diseases: a population-based study using UK primary care data

ABSTRACT

Risks for cardiovascular diseases (CVDs) other than myocardial infarction and stroke in the general COPD population are not well quantified. We used a matched cohort study design and Cox regression to estimate relative risks for 12 separate CVDs in a large population-based cohort of patients with COPD over a 12-year period. Associations between COPD and individual CVDs were heterogeneous, with the highest relative risks observed for heart failure and diseases of the arterial circulation (in excess of 2.5 for those aged 64–75 years). Relative risks declined with increasing age but for most CVD outcomes remained unchanged over the study period.

INTRODUCTION

Investigation of cardiovascular disease (CVD) risks in people with chronic obstructive pulmonary disease (COPD) has focused on coronary heart disease, in particular myocardial infarction (MI), and stroke.[1–3] Risks for other CVDs such as angina, atrial fibrillation, heart failure and diseases of the arterial circulation are less well documented, but evidence is accumulating that these too are elevated in COPD.[4–7] By using UK electronic primary healthcare records (Clinical Practice Research Datalink, CPRD), we have estimated relative risks for 12 separate CVD outcomes in a large population-based cohort of patients with COPD over a 12-year period.

METHODS

A dynamic cohort of all patients with a general practitioner (GP) diagnosis of COPD prior to 31 December 2015 was drawn from CPRD using a validated algorithm.[8] Exclusion criteria as well as the criteria used to define the start and end of each person's follow-up are detailed in the online supplementary appendix 1. Individuals were assigned a smoking status (never, ex, current) based on information recorded in CPRD closest to their COPD diagnosis date.

We defined 12 CVD outcomes—abdominal aortic aneurysm (AAA), angina, atrial fibrillation, heart failure, MI, peripheral artery disease (PAD), pulmonary artery hypertension (PAH), stroke (subdivided into all stroke excluding transient ischaemic attacks (TIAs), ischaemic stroke, haemorrhagic stroke and TIAs) and sudden cardiac arrest—and identified incident cases using Read codes.

In the first part of our analysis, we estimated age-specific and gender-specific incidence rates for each of these 12 CVDs in people with a diagnosis of COPD. We then used a matched cohort study design and a Cox regression model to estimate relative risks for the same 12 CVDs, comparing people with and without COPD. In our primary analysis, we adjusted for sex and GP practice by matching and stratified our results by age group and calendar time (using three 4-year consecutive time periods 2004–2007, 2008–2011, 2012–2015). In a secondary analysis, we also adjusted for smoking. A more detailed description of the methodology is provided in the online supplementary appendix 1. All statistical analyses were conducted using Stata V.14 (StataCorp, Texas, USA).

RESULTS

A total of 299 039 individuals with at least one specific COPD code in their primary healthcare record were identified, of whom 209 909 satisfied our inclusion criteria. The number of people identified equates to a UK COPD prevalence of 2%–3%, in line with expectations.

The characteristics of the base COPD cohort are summarised in table 1. In this population, the risk of developing CVDs generally increased with age. However, there was little evidence to suggest that incidence rates have altered substantially over the last decade (online supplementary appendix 2: figure A2.1).

Relative risks (expressed as HRs) for all CVD subtypes decreased with increasing age; the inverse relationship between relative risk for CVD and increasing age was especially pronounced for atrial fibrillation, heart failure, coronary heart disease (angina, MI) and stroke outcomes (figure 1). In the crude analysis (in which adjustment was made for matching variables only), we found no evidence of an association between COPD and any of our four stroke outcomes in the oldest age

Table 1 Characteristics of the base* COPD cohort

	All subjects	Men	Women
	n (% unless otherwise stated)	n (% unless otherwise stated)	n (% unless otherwise stated)
All ages	209 909	109 406	100 503
Age group			
Under 55 years	44 553 (21.2)	22 338 (20.4)	22 215 (22.1)
55–64 years	55 467 (26.4)	29 766 (27.2)	25 701 (25.6)
65–74 years	58 721 (28.0)	31 606 (29.0)	27 115 (27.0)
75–85 years	42 081 (20.1)	21 575 (19.7)	20 506 (20.4)
Over 85 years	5937 (4.3)	4121 (3.8)	4966 (4.9)
Mean age at COPD diagnosis (years; SD)	65.84 (11.7)	65.72 (11.4)	65.98 (12.0)
Smoking status			
Never smoker	5520 (2.6)	2061 (1.9)	3459 (3.4)
Ex-smoker	96 680 (46.1)	56 141 (51.3)	40 536 (40.3)
Current	89 505 (42.6)	44 678 (40.8)	44 827 (44.6)
Unknown	18 204 (8.7)	6526 (6.0)	11 678 (11.6)

*In order to compute relative risk for each of our 12 CVD outcomes, a series of 12 matched cohorts were created in which subjects who experienced the CVD in question prior to their diagnosis of COPD were excluded before being matched to a COPD-free control. The base cohort thus comprises all individuals with COPD meeting study inclusion criteria, save any subsequent exclusions for a prior CVD event.

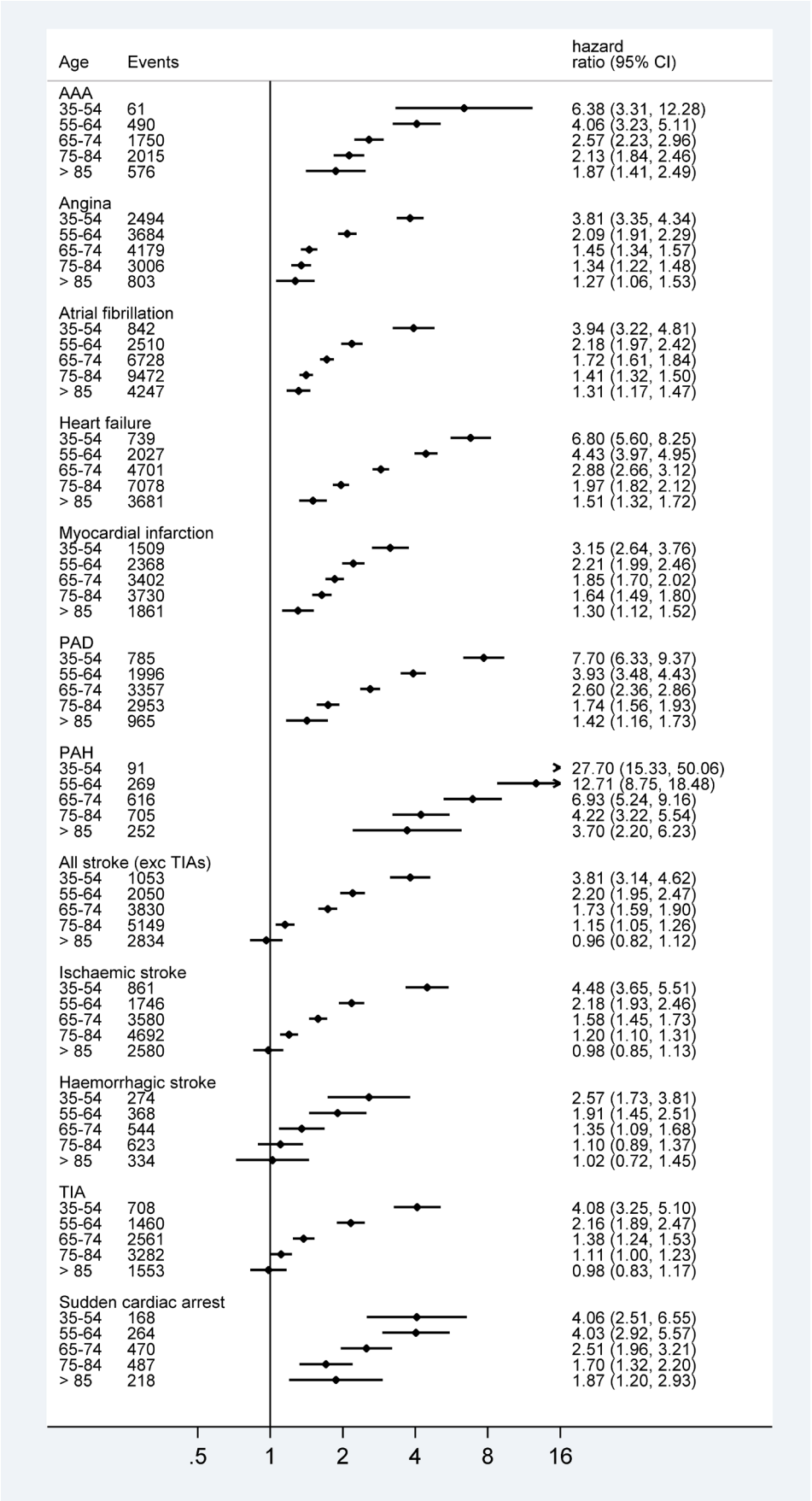

Figure 1 HRs for 12 cardiovascular disease outcomes, by age group, comparing people with and without COPD (HRs are derived from Cox proportional hazard models adjusted for sex and GP practice by matching only).

group. For all other outcomes, the excess risk was evident at all ages. For most CVD outcomes, relative risks remained unchanged over the study period (supplementary appendix 2: figureA2.2).

DISCUSSION

We have shown that increased risks for CVD in people with COPD are not confined to MI and stroke, but exist across the spectrum of CVD subtypes. We further demonstrated that while relative risks for CVDs vary by age, these risks do not appear to have materially altered over the 12-year period of our study, implying that people with COPD are still at a disadvantage in terms of CVD risks compared with their COPD-free counterparts.

While in line with the findings of other studies, the inverse relationship between relative risk and age is a striking feature of our analysis (figure 1),[9] and suggests that in older age CVD risk is driven more by the mechanisms of ageing than by COPD per se. It is not clear why relative risk for CVD should be higher among younger patients with COPD. It is possible that this high-risk group represents a subset of susceptible individuals who as a consequence of a low maximally attained lung function develop airflow limitation (and thus COPD) at a relatively early age. Factors that contribute to poor lung function in this group, such as low birth weight and environmental exposures, may well also be contributing to an increased risk for CVD in middle age.

We found a considerable degree of heterogeneity in the magnitude of the relative risks across the individual CVD outcomes studied. While COPD was associated with an increased risk of all 12 outcomes, the highest HRs were observed for AAA, PAD, PAH and heart failure. These patterns mirror those reported by Chen *et al*[1] who also ranked diseases of the pulmonary circulation and heart failure among the more 'high-risk' outcomes in a meta-analysis of the prevalence of CVD comorbidities in COPD. Our heterogeneity patterns are also similar to those reported for the association between smoking and the initial (first) presentation of specific CVD outcomes by Pujades-Rodriguez *et al*.[10]

Large sample size and a representative population-based COPD cohort identified using a validated algorithm with a high positive predictive value are the key strengths of our study design. Limitations include difficulties in characterising smoking status, differential misclassification of CVD outcomes and lack of adjustment for other potential confounders (online supplementary appendix 3).

Taken together, our findings provide a strong case for a more aggressive management of CVD risks in COPD that is not confined to MI and stroke but extends to other conditions such as atrial fibrillation, heart failure and PAD. Our study also adds to the growing body of evidence that supports calls for a more integrated approach to the diagnosis and management of lung and heart disease, which targets those in middle to late-middle age.

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Contributors LS and JKQ served as principal investigators and conceived and designed the study; ADM conducted the data analysis and drafted the manuscript; KJR and KB provided statistical support and assisted with the data analysis; all co-authors read and commented on earlier versions of the manuscript.

Funding This work was conducted as part of a research degree funded by The British Lung Foundation (RG14-15). LS is supported by a Wellcome Senior Clinical Fellowship. KB holds a Sir Henry Dale fellowship jointly funded by the Wellcome Trust and the Royal Society.

Competing interests None declared.

Ethics approval The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol no. 15_114R) and the approved protocol was made available to the journal and reviewers during peer review. Generic ethical approval for observational research using the CPRD with approval from ISAC has been granted by a Health Research Authority (HRA) Research Ethics Committee (East Midlands—Derby, REC reference no. 05/MRE04/87). The study also has the approval of the London School of Hygiene and Tropical Medicine (LSHTM) Ethics Committee (No. 7611).

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2017-210865).

To cite Morgan AD, Rothnie KJ, Bhaskaran K, *et al*. *Thorax* 2018;**73**:877–879.

Received 5 August 2017
Revised 11 January 2018
Accepted 15 January 2018
Published Online First 3 February 2018

► http://dx.doi.org//10.1136/thoraxjnl-2018-211553

Thorax 2018;**73**:877–879.
doi:10.1136/thoraxjnl-2017-210865

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