EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

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Original article

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Please cite this article as: Whittaker HR, Bloom C, Morgan A, *et al*. Accelerated FEV_1 decline and risk of cardiovascular disease and mortality in a primary care population of COPD patients. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.00918-2020).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Accelerated FEV_1 decline and risk of cardiovascular disease and mortality in a primary care population of COPD patients

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Word count: 3,990

This article has an online data supplement.

Take home message

In a primary care population of COPD patients, CVD outcomes and mortality were not associated with accelerated FEV_1 decline but with frequent and severe exacerbations of COPD and increased breathlessness.

Abstract

Accelerated lung function decline has been associated with increased risk of cardiovascular disease (CVD) in a general population, but little is known about this association in chronic obstructive pulmonary disease (COPD). We investigated the association between accelerated lung function decline and CVD outcomes and mortality in a primary care COPD population.

COPD patients without a history of CVD were identified in the Clinical Practice Research Datalink (CPRD-GOLD) primary care dataset (n=36,282). Accelerated FEV_1 decline was defined using the fastest quartile of the COPD population's decline. Cox regression assessed the association between baseline accelerated FEV_1 decline and a composite CVD outcome over follow-up (myocardial infarction, ischaemic stroke, heart failure, atrial fibrillation, coronary artery disease, and CVD mortality). The model was adjusted for age, gender, smoking status, BMI, history of asthma, hypertension, diabetes, statin use, mMRC dyspnoea, exacerbation frequency, and baseline FEV_1 percent predicted.

6,110 (16.8%) COPD patients had a CVD event during follow-up; median length of follow-up was 3.6 years [IQR 1.7 – 6.1]). Median rate of FEV_1 decline was –19.4ml/year (IQR, –40.5 to 1.9); 9,095 (25%) patients had accelerated FEV_1 decline (> –40.5ml/year), 27,287 (75%) did not (≤ –40.5ml/year). Risk of CVD and mortality was similar between patients with and without accelerated FEV_1 decline (HR_{adj} 0.98 [95%CI, 0.90–1.06]). Corresponding risk estimates were 0.99 (95%CI 0.83-1.20) for heart failure, 0.89 (95%CI 0.70-1.12) for myocardial infarction, 1.01 (95%CI 0.82-1.23) for stroke, 0.97 (95%CI 0.81-1.15) for atrial fibrillation, 1.02 (95%CI 0.87-1.19) for coronary artery disease, and 0.94 (95%CI 0.71-1.25) for CVD mortality. Rather, risk of CVD was associated with mMRC score≥2 and ≥2 exacerbations in the year prior.

CVD outcomes and mortality were associated with exacerbation frequency and severity and increased mMRC dyspnoea but not with accelerated FEV_1 decline.

Introduction

Forced expiratory volume in 1 second (FEV_1) declines with age from early adulthood. A previous meta-analysis found that in the general population the average rate of FEV_1 decline in aging adults ranged from –9.9ml/year to –56.0ml/year with a median decline of –29.4ml/year[1]. Patients with chronic obstructive pulmonary disease (COPD) however lose lung function at an accelerated rate, at approximately –33.2ml/year according to Vestbo et al. The rate of decline in COPD is highly heterogeneous, with approximately 38% of patients declining by more than –40ml/year, 31% at rates between –21ml/year and –40ml/year, and 31% by less than –21ml/year[2]. Several factors have been found to be associated with the rate of change in lung function in COPD patients including frequency and severity of acute exacerbations of COPD (AECOPD), smoking, and COPD severity [3-8]. However, little is known about the association between the rate of lung function decline and comorbidity in COPD patients.

One of the most prevalent comorbidities in COPD patients is cardiovascular disease (CVD) [9]. Both COPD and CVD share common risk factors such as smoking and aging [10, 11]. Specifically, exposure to toxic particles in cigarette smoke can cause the increased systemic inflammation that characterises both COPD and CVD [12, 13]. It is not fully understood how COPD and CVD are linked beyond their shared risk factors but researchers have identified a number of possible mechanisms such as hypoxia and oxidative stress that might be involved[9, 10]. Furthermore, numerous studies have reported the existence of associations between various measures of impaired lung function, including low FEV_1, FVC and FEV_1/FVC, and an increased likelihood of developing CVD, as well as an increased risk of hospitalisation and death secondary to CVD[14-20].

More recently, it has been suggested that the rate at which lung function is lost be associated with increased risk of CVD. In a general population study of participants in the Atherosclerosis Risk in Communities (ARIC) study, accelerated decline in FEV_1, over a baseline period of three years, was

associated with an increased risk of hospitalisation and death from heart failure and stroke [21]. To date, no studies have investigated the association between rate of FEV_1 decline and risk of CVD outcomes and mortality in patients with COPD, who are already at greater risk of CVD than the general population [9]. We therefore investigated whether COPD patients with accelerated FEV_1 decline were more likely to develop CVD in a primary care population of COPD patients in England.

Methods

Study population and design

Clinical Practice Research Datalink (CPRD)-GOLD is a primary care electronic healthcare record database. It contains information on general practitioner (GP) practices in the UK including information on consultations, patient demographics, therapies prescribed, and clinical diagnoses. CPRD contains approximately 7% of the UK's population and is generalizable in terms of age, sex, and ethnicity [22]. Linked pseudonymised data from Hospital Episode Statistics (HES) and the Office of National Statistics (ONS) were provided for this study by CPRD for patients in England. Data was linked by NHS Digital using identifiable data held only by NHS Digital. General practices consent to this process at a practice level, with individual patients having the right to opt-out. HES and ONS data were used to identify CVD hospitalisations and deaths.

Patients were included if they met the following minimum inclusion criteria: (i) patients were eligible for HES linkage; ii) diagnosed with COPD; iii) aged 35 or older; iv) current or ex-smokers; and v) had data recorded from 2004 onwards. Specifically, the inclusion date was the date of patients' first FEV_1 measurement after the date at which they were diagnosed with COPD, registered with their current GP, aged 35 years, and the date at which the practice was deemed of research quality [22] (**figure 1**).

Following the inclusion date, patients were required to have 3 years of baseline follow-up with at least 2 FEV_1 measurements at least 6 months apart in order to estimate the patient's rate of FEV_1 decline as changes in lung function should be estimated over longer periods of time in order to draw conclusions about long term lung function decline and to reduce possible measurement error [23]. The index date was the date at the end of the baseline period and indicated the start of follow-up (**figure 1**). Patients were consequently followed up from their index date until the 31st December 2017 or the first date of any of the following events: transferred to a non-CPRD GP practice, the last data collection date, died from non-CVD causes, or had a CVD event. In addition, patients were required to have no history of stroke, heart failure, myocardial infarction, atrial fibrillation, and coronary artery disease ever recorded prior to the index date.

COPD and FEV_1 decline

Patients with COPD were identified using a validated algorithm for COPD in CPRD-GOLD [24]. Patients aged 35 years and over who had at least one record denoting a clinical diagnosis of COPD and a history of smoking (ex or current) were considered to have COPD. Never smokers were excluded due to the potential misclassification of COPD with asthma. The exposure of interest was accelerated FEV_1 decline. For each study eligible patient, all absolute FEV_1 measurements recorded in CPRD-GOLD between the inclusion date and the index date were identified and the rate of FEV_1 decline estimated using mixed linear regression modelling with random intercepts and random slopes. Accelerated decline was defined as patients whose FEV_1 decline fell in the fastest quartile of the decline. Patients were classed as those with accelerated FEV_1 decline or patients without accelerated FEV_1 decline. In a recent validation study, the quality of spirometry measurements was found to be high [25].

Cardiovascular disease outcomes

The primary outcome was a composite measure defined as the time to first CVD event during follow-up and comprised of myocardial infarction, heart failure, stroke, atrial fibrillation, coronary artery disease excluding acute myocardial infarction, and CVD mortality. These events were identified through primary care records (CPRD-GOLD), hospital admissions data (HES), and mortality statistics (ONS). ICD-10 codes were used to identify hospitalisations (primary diagnosis) and CVD deaths. CVD events that were recorded on the same day in CPRD-GOLD, HES, and/or ONS were further explored to avoid duplication of events. In these cases, mortality events were prioritised, followed by hospitalisations, and then GP-recorded events. Secondary outcomes included time to first myocardial infarction, heart failure, stroke, atrial fibrillation, coronary artery disease, and CVD mortality.

Statistical analyses

Baseline characteristics were described using proportions, medians, and interquartile ranges (IQR). Cox regression was used to investigate time to the first composite CVD event, comparing patients with and without accelerated FEV_1 decline, adjusted for gender, age (continuous), smoking status (current or ex-smoker), and level of airflow obstruction (mild: FEV_1 ≥80% predicted; moderate: FEV_1 50–80% predicted; severe: FEV_1 30-–50% predicted; very severe: FEV_1 <30% predicted , based on patients' last baseline FEV_1 measurement, height, and gender), which were identified at index date. Modified MRC dyspnoea (0–4), and BMI (underweight, normal, overweight, obese) were defined as the closest measurement to the index date within the baseline period of three years. History of hypertension, diabetes, and asthma were identified within the baseline period of three years. Statin use was defined as at least one prescription in the year prior to the index date. AECOPD frequency and severity was also defined using information recorded in the year prior to the index date, and categorised as: none; 1 moderate (GP-recorded AECOPD) and 0 severe (hospitalisation for AECOPD);

2 moderate and 0 severe; 3 or more moderate and 0 severe; 1 severe and any number of moderate; and 2 or more severe and any number of moderate AECOPD. This categorisation was similar to that used in previous investigations of AECOPD events in CPRD-GOLD [26]. Secondary analyses investigated the association between accelerated FEV_1 decline and each separate CVD, i.e. myocardial infarction, heart failure, stroke, atrial fibrillation, coronary artery disease, and CVD mortality.

The following sensitivity analyses were also performed: 1) rates of relative change in FEV_1 and change in FEV_1 percent predicted were used to categorise accelerated decline (as opposed to absolute FEV_1); 2) risk of CVD outcomes and mortality was compared between patients with accelerated FEV_1 decline and patients in the other three quartiles separately; 3) the linear relationship between rate of FEV_1 decline and risk of CVD was investigated; 4) different cut offs were used (>-20ml/year (reference group), -20 to -40ml/year, -40 to -60ml/year, and <-60ml/year) to define four groups of rates of FEV_1 decline; 5) spline regression was used to assess non-linear relationships between accelerated FEV_1 decline and risk of CVD outcomes using 10^{th}, 50^{th}, and 90^{th} percentiles of FEV_1 decline; 6) patients with a history of asthma were excluded in case of misclassification of COPD; 7) only hospitalised CVD events were investigated as the outcome; 8) only GP recorded CVD outcomes were investigated as the outcome; 9) only deaths from CVD were investigated as the outcome; 10) models were stratified by gender, age, smoking status, AECOPD frequency, and airflow obstruction (i.e. baseline FEV_1 percent predicted); 11) accelerated FEV_1 decline was categorised using rate of FEV_1 decline that was estimated using at least 4 FEV_1 measurements during the baseline period; 12) accelerated FEV_1 decline was categorised using rate of FEV_1 decline that was estimated using at least 2 FEV_1 measurements at least 2 years apart; 13) the association between accelerated FEV_1 decline and risk of composite CVD, heart failure, myocardial infarction, stroke, atrial fibrillation, and coronary artery disease in the first year of follow-up; and 14)

all CVD events during follow-up were identified (not first event only) and Poisson regression was used to model repeated events. All analyses were performed using STATA v16.0.

Results

Patient characteristics

We identified a total of 132,923 patients in CPRD-GOLD who met our minimum eligibility criteria. After applying further inclusion criteria, a total of 36,382 patients were included in the final study population (see **Figure 2)**. The median follow-up time was 3.6 years (IQR, 1.7–6.1). The median rate of FEV_1 decline was –19.4ml/year (IQR, –40.5 to 1.9) and thus patients were categorised as having accelerated FEV_1 decline if they had an FEV_1 decline faster than –40.5ml/year. This meant that 9,095 (25%) of patients were classed as having accelerated decline and 27,287 (75%) were classed as non-accelerated decliners. Patients had a median of 3 (IQR, 2-4) FEV_1 measurements over the three-year baseline period. **Figure E1 and E2** illustrate the number of FEV_1 measurements and time intervals between measurements during the baseline period.

Table 1 reports baseline characteristics for patients with and without accelerated FEV_1 decline. Patients with accelerated decline were more likely to be male, have severe airflow obstruction (lower FEV_1 percent predicted), be current smokers, but less likely to have hypertension. Patients were similar in terms of all other CVD characteristics (diabetes and statin use).

Risk of Cardiovascular Disease

During follow-up 6,110 patients had a CVD event, which equates to a rate of 4.6 events per 100

person-years (95% CI, 4.5 – 4.7). We found no evidence of an association between risk of composite CVD events and accelerated FEV_1 decline, in either our unadjusted analysis (HR_{unadj}=0.99(95%CI, 0.93–1.05) or in a fully adjusted analysis (HR_{adj}=0.98(95%CI, 0.90–1.06); see **Figure 3).** We did however, find evidence of an association between increased frequency and severity of AECOPD and breathlessness (mMRC) and CVD outcomes (see **Figure 3)**. In addition, increasing age, male gender, current smokers, patients with hypertension, and patients using statins were at increased risk for CVD events compared to reference groups (see **Table E1**).

Of 6,110 patients who had a CVD event during follow up, 1,220 were recorded as having had heart failure, 788 a myocardial infarction, 1,039 a stroke, while 1,427 were diagnosed with atrial fibrillation, and 1,636 with coronary artery disease. In addition, 556 events were CVD related deaths. There was no association between accelerated FEV1 decline and heart failure (HR_{adj} 0.99 (95% CI 0.83-1.20)), myocardial infarction (HR_{adj} 0.89 (95% CI 0.70-1.12)), stroke (HR_{adj} 1.01 (95% CI 0.82-1.23)), atrial fibrillation (HR_{adj}0.97 (95% CI 0.81-1.15), coronary artery disease (HR_{adj}1.02 (95% CI 0.87-1.19)), and CVD mortality (HR_{adj}0.94 (95% CI 0.71-1.25)) (see **Figure 4).** Whilst no association was seen between accelerated FEV_1 decline and risk of individual CVD outcomes, increased frequency and severity of AECOPD, and increased mMRC were both associated with all CVD outcomes individually in unadjusted models. **Tables E2-E7** provide hazard ratios for all covariates in each model for heart failure, myocardial infarction, stroke, atrial fibrillation, and coronary artery disease, respectively.

Sensitivity analyses

Risk of CVD was similar between patients with and without accelerated decline irrespective of the definitions and cut-offs used to categorise patients according to their rate of loss of lung function (FEV_1). This finding remained unchanged when accelerated decline was quantified in terms of FEV_1 percent predicted or relative change in FEV_1 from baseline, and there was no association between

linear rate of FEV_1 decline and risk of CVD (**Table E8**). In addition, there was no difference in risk of CVD between patients with FEV_1 decline in the slowest quartile and all other quartiles (**Table E8**), between patients with FEV_1 decline > –20ml/year and patients with FEV_1 decline in the range –20 to –40ml/year, –40 to –60ml/year, and < –60ml/year (**Table E9**), and between accelerated and non-accelerated FEV_1 decline using spline regression (**Figure E3**).

When the analysis was restricted to COPD patients without a history of asthma, there was no difference in CVD risk between patients with and without accelerated FEV_1 decline (**Table E10**). Similarly, restricting the analysis to events recorded in primary care (GP-diagnosed CVD) and to hospitalisations for CVD did not materially affect our effect estimates (**Table E11**). In addition, no association was seen between accelerated FEV_1 decline and risk of cardiovascular disease and mortality after stratification by gender, age, smoking status, AECOPD frequency, and airflow obstruction (baseline FEV_1% predicted) (**Table E12**).

Including only those patients who had at least four FEV_1 measurements and only those with at least two FEV_1 measurements at least 2 years apart, also produced no appreciable change in the HRs for the association between accelerated FEV_1 decline and CVD risk (**Tables E13 and E14**). Nor did we observe an association between accelerated FEV_1 decline and risk of heart failure, myocardial infarction, stroke, atrial fibrillation, and coronary artery disease, either as separate outcomes or a composite outcome in the first year of follow-up (**Figure E4**). Finally, in a sensitivity analysis where we allowed for multiple CVD events during follow up (rate = 9.5 events per 100 person-years (95%CI, 9.2–9.8)) we found that the rate of composite CVD , and its individual components, were similar between patients with and without accelerated FEV_1 decline (**Figure E5**).

Discussion

This is the first large observational study to investigate the association between accelerated FEV_1 decline and risk of CVD outcomes and mortality in COPD. We found that in CVD-naive patients, those with accelerated FEV_1 decline had a similar risk of CVD outcomes and mortality compared to patients without accelerated decline, regardless of type of CVD. Rather, we found that other disease characteristics were more closely related to CVD outcomes and mortality, including history of frequent moderate and severe AECOPD and increased breathlessness.

Previous studies

No previous studies have investigated the relationship between lung function decline and CVD in a COPD population. A recently published study by Silvestre and colleagues investigated this relationship in a general population of people living in USA using the ARIC study [21]. The authors found that people with accelerated FEV_1 decline had a greater risk of CVD compared to those without accelerated decline over a 17-year period. CVD was defined as a composite endpoint that included hospitalisation or death from heart failure, stroke, and coronary heart disease, including myocardial infarction. When each CVD component was analysed separately, they found accelerated FEV_1 decline was most strongly associated with heart failure and stroke events but not with coronary heart disease events.

Many differences exist between our study and that of Silvestre et al. that could explain the differences observed. ARIC is a cohort study that followed participants from 1987 in order to understand the causes of atherosclerosis and other clinical outcomes, including CVD risk factors. Data for these participants was collected systematically at four phases during follow-up by trained healthcare staff. This differs from CPRD-GOLD, a routinely collected healthcare database of information recorded at primary care GP practices across the UK. Whilst there are merits to both

types of databases, study results are likely to differ. Furthermore, Silvestre et al. used relative change in FEV_1 percent predicted from baseline to estimate accelerated FEV_1 decline. Our study used absolute change in FEV_1 adjusting for baseline FEV_1. Additionally, we performed sensitivity analyses using change in FEV_1 percent predicted and relative change in absolute FEV_1 and findings were consistent with our main results. Lastly, whilst Silvestre et al adjusted for baseline FEV_1, other diagnoses such as COPD or airflow obstruction were not accounted for. It is possible that patients with COPD were confounding the relationship between rate of FEV_1 decline and CVD outcomes. It is also important to note that the magnitude of association with CVD outcomes, between people with and without accelerated $FEV_{1,}$ was small in the Silvestre et al study suggesting a marginal increase in their risk (HR_{adj}=1.14 (95% CI 1.06–1.23)).

Other studies have found that low lung function (both FEV_1 and FVC) in early adulthood is associated with risk of CVD in later life in general populations [14, 18-20]. For example, participants enrolled in the ARIC study in the lowest quartile had an increased risk of incident hospitalisation or death from heart failure compared with those in the highest quartile. This risk of was also higher in participants with airflow obstruction (FEV_1/FVC<70%) compared to those without, in both men and women [14]. Again, this is likely driven by COPD patients who generally have a lower FEV_1 compared to healthy individuals of the same age. Similarly, the Health, Aging and Body Composition (ABC) study and the Coronary Artery Risk Development in Young Adults (CARDIA) study, two US community- based studies, found linear associations between FEV_1 percent predicted and incident heart failure and stroke hospitalisations [15, 16]. Overall however, there is little evidence to suggest that low lung function, compared to high lung function, in patients with COPD is associated with CVD outcomes and mortality. Recently, a post-hoc analysis of (SUMMIT) trial data found that FEV_1 percent predicted was not associated with CVD events in a COPD population who were at an increased risk of CVD [27]. This is in line with our adjusted findings where baseline FEV_1 percent predicted was not

associated with risk of CVD and mortality. The association between FEV_1, FEV_1 decline and CVD differs between non-COPD general populations and COPD populations.

Exacerbations of COPD, mMRC, and CVD

Interestingly, increasing frequency and severity of AECOPD and mMRC were associated with increased risk of CVD outcomes and mortality in our COPD patient cohort. This suggests that other markers of disease severity, rather than rate of lung function decline, might be more closely related to CVD outcomes and mortality [28]. This observation is in keeping with previous observational studies which have demonstrated that the period immediately following an AECOPD are extremely high risk for CVD events such as myocardial infraction and stroke relative to periods of more stable disease. For example, Rothnie et al. used linked UK primary care data (CPRD-GOLD and HES) to investigate the relationship between AECOPD (both moderate and severe) and myocardial infraction and stroke (up to 91 days after an AECOPD) [29]. The risk of myocardial infarction and stroke increased after an AECOPD and was higher in patients with more severe AECOPD. Another observational UK study of primary care patients (THIN database) found that people with COPD had a higher risk of myocardial infarction for up to 5 days after an AECOPD [30]. Likewise, a post-hoc analysis of data from the SUMMIT study reported an association between AECOPD and increased risk of CVD outcomes (including death, myocardial infarction, stroke, angina, transient ischemic attack) for up to 1 year after an AECOPD, which was heightened after severe AECOPDs [31].

Few studies have investigated the long-term association between AECOPD frequency and CVD outcomes. One study by Windsor et al. used UK primary care GP data (CPRD-GOLD) to perform a case–control study that compared the odds of having a stroke in frequent (≥2 AECOPD in the year prior to index date) and infrequent exacerbators. They found no relationship between AECOPD

frequency and stroke over a maximum of 9 years [32]. However, this study did not use secondary care data, leading to potentially significant misclassification as they were not able to include more severe AECOPD or strokes. A previous validation study highlights the importance of using linked secondary care data with CPRD for identifying events [33], may have resulted in potentially significant event misclassification. In particular, the Windsor et al study may well have missed a substantial proportion more severe AECOPD or strokes. In contrast, our study, which employed a cohort design in HES and CPRD-GOLD linked data, found that both frequency and severity of AECOPD were strongly associated with risk of CVD outcomes over a maximum follow-up of 13 years.

Strengths and limitations

This is the first study to investigate the relationship between rate of lung function decline and risk of CVD outcomes in a COPD population. Using electronic healthcare records, we were able to identify a large population (N=132,923) of COPD patients with varying degree of disease severity creating a more generalisable population of COPD patients. We included a wide range of CVD end points (both moderate and severe based on GP treated or hospitalised CVD events) in order to capture the varying degree of CVD event severities. Whilst change in absolute FEV_1 was our main exposure, following previous studies on lung function decline, we included baseline FEV_1 percent predicted as a confounder in our model and performed a sensitivity analysis using relative change in FEV_1 [2, 34, 35]. Similarly , due to high within patient variation in absolute FEV_1, research suggests that FEV_1 percent predicted is better at estimating change in lung function in studies with follow-up less than 5 years[36]. We performed a sensitivity analyses using change in FEV_1 percent predicted and results were consistent with those of our main analysis.

In order to determine rate of lung function decline at baseline, minimise the effect of measurement error, and accurately summarise a patient's lung function decline, patients were required to have at least three years of baseline follow-up prior to the start of follow-up following previous research [21]. Therefore, this design could have caused immortal time bias. Also, baseline trajectories are likely to remain, and it is unlikely that anything disease modifying would change patient's trajectory from accelerated decline to non-accelerated decline, nor would this influence risk of CVD given no association found in this study. In addition, it is possible that patients with COPD could have been misdiagnosed with asthma and vice versa. This is more common in patients over the age of 40 [37]. This is a limitation of the data as we depend on diagnoses and symptoms recorded by the GP. We performed a sensitivity analysis to attempt to exclude patients who might have been misdiagnosed with COPD. Furthermore, not all patient characteristics or lifestyle factors are recorded within primary and secondary care, such as physical exercise. Therefore, residual confounding is likely. Lastly, statin use was used as a proxy for cholesterol level and pack years smoking was not used due to its poor reliability. Despite this, robust sensitivity analyses were consistent with the main findings.

Conclusion

We have conducted the first observational study to investigate the relationship between accelerated FEV_1 decline and risk of CVD outcomes and mortality in COPD patients. We found no association between rate of FEV_1 decline and composite CVD outcomes or heart failure, myocardial infarction, stroke, atrial fibrillation, and coronary artery disease excluding myocardial infarction as separate outcomes. In contrast, frequent and severe AECOPD and increased breathlessness were associated with risk of CVD outcomes and mortality.

Word count: 3,990

Acknowledgements

The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol number 19_258) and the approved protocol was made available to the journal and reviewers during peer review. This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. Linked pseudonymised data was provided for this study by CPRD. Data is linked by NHS Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select general practices consent to this process at a practice level with individual patients having the right to opt-out.

This study is based in part on data from the Clinical Practice Research Datalink (CPRD) obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the National Health Service (NHS) as part of their care and support. The Office for National Statistics (ONS) was the provider of the ONS Data contained within the CPRD Data and maintains a Copyright © 2019, re-used with the permission of The Health & Social Care Information Centre, all rights reserved. The interpretation and conclusions contained in this study are those of the authors alone.

Data are available on request from the Clinical Practice Research Datalink (CPRD). Their provision requires the purchase of a license and our license does not permit us to make them publicly available to all. We used data from the version collected in January 2018 and have clearly specified the data selected in our Methods section. To allow identical data to be obtained by others, via the purchase of a license, we will provide the code lists on request. Licences are available from the CPRD (http://www.cprd.com): The Clinical Practice Research Datalink Group, The Medicines and Healthcare products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU.

This research was supported by the NIHR Imperial Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

HRW reports grants from GSK, AZ, and BI, outside the submitted work; CB reports funding from AZ, Chiesi, and Asthma UK, outside the submitted work; ADM has nothing to disclose; DJ reports grants from European Union and Cystic Fibrosis Trust, outside the submitted work; SJK reports grants from Medical Research Council during the conduct of the study and personal fees from Roche Diagnostics and DIADEM, outside the submitted work; JKQ reports grants from British Lung Foundation, during the conduct of the study and grants and personal fees from AZ, Asthma UK, BI, Bayer, GSK, MRC, and Chiesi, outside the submitted work.

Funding

This work was funded by the British Lung Foundation.

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Figure 1: Study design

Figure 2: Patients meeting inclusion criteria

Figure 3: Hazard ratios (95% CI) illustrating the association between accelerated FEV_1 decline, AECOPD frequency, mMRC and risk of CVD outcomes and mortality.

Figure 4: Hazard ratios (95% CI) illustrating the association between accelerated FEV_1 decline, AECOPD frequency, mMRC and risk of a) heart failure, b) myocardial infarction, c) stroke, d) atrial fibrillation, e) coronary artery disease, and f) CVD mortality.

Table 1: Baseline characteristics of patients with and without accelerated FEV_1 decline. Numbers are n (%) or median (IQR).

Table 1: Baseline characteristics of patients with and without accelerated FEV_1 decline. Numbers are n (%) or median (IQR).

Baseline characteristics	Non-accelerated FEV_1 decline n=27,287	Accelerated FEV_1 decline n=9,095
Males	12,942 (47.4)	5,381 (59.2)
Age	68.9 (61.7 – 76.1)	66.8 (59.6 – 74.0)
Smoking status		
Current smokers	16,912 (62.0)	6,013 (66.1)
Ex-smokers	10,375 (38.0)	3,082 (33.9)
Airflow obstruction*		
Mild	7,566 (27.9)	1,567 (17.4)
Moderate	11,771 (43.5)	3,851 (42.7)
Severe	6,321 (23.3)	2,801 (31.0)
Very severe	1,424 (5.3)	804 (8.9)
AECOPD		
None	10,954 (40.1)	3,496 (38.4)
1 moderate, 0 severe	6,478 (23.7)	2,031 (22.3)
2 moderate, 0 severe	3,730 (13.7)	1,278 (14.1)
≥3 moderate, 0 severe	4,703 (17.2)	1,697 (18.7)
1 severe, any moderate	1,116 (4.1)	466 (5.1)
≥2 severe, any moderate	306 (1.1)	127 (1.4)
mMRC*		
0	3,797 (20.9)	1,206 (20.2)
1	7,396 (40.6)	2,289 (38.4)
2	4,448 (24.4)	1,526 (25.6)
3	2,196 (12.1)	784 (13.1)
4	365 (2.0)	160 (2.7)
BMI*		
Underweight	1.181 (4.9)	390 (4.9)
Normal	8,089 (33.6)	2.750 (34.6)
Overweight	8,060 (33.5)	2,628 (33.1)
Obese	6,727 (28.0)	2,180 (27.4)
Hypertension	11,770 (43.1)	3,660 (40.2)
Diabetes	3,040 (11.1)	974 (10.7)
Asthma	11,238 (41.2)	3,566 (39.2)
Statin use	8,350 (30.6)	2,774 (30.5)

*Airflow obstruction N=36,105; mMRC N=24,167; BMI N=32,005.

Figure 1: Study design

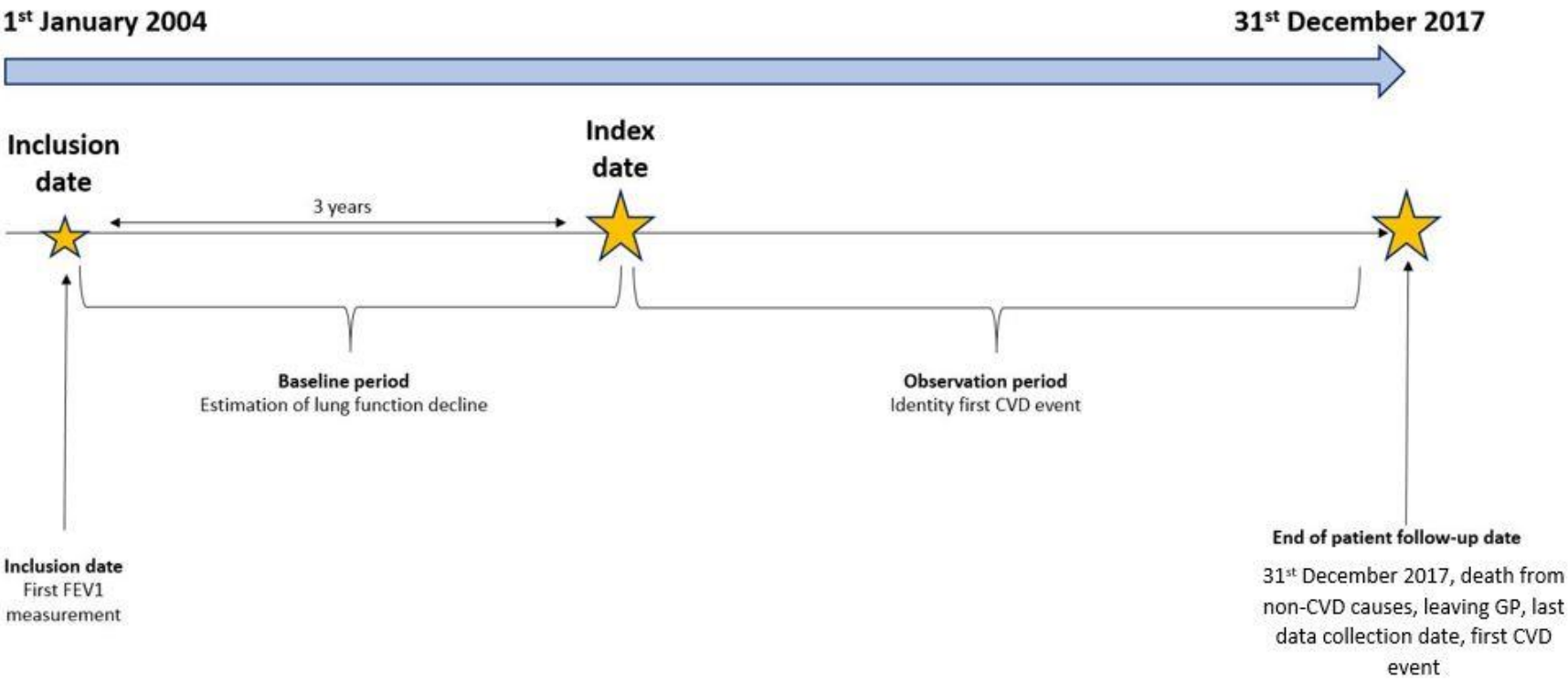
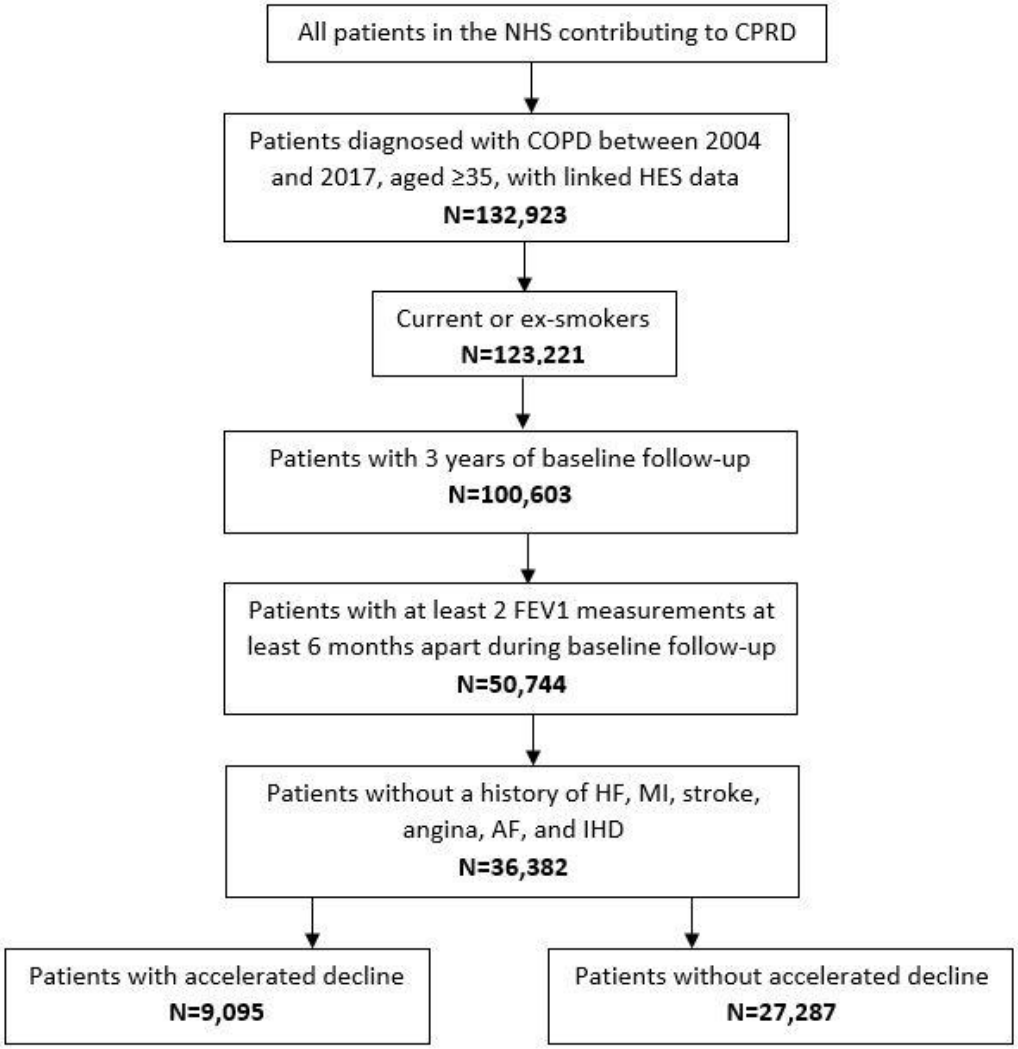
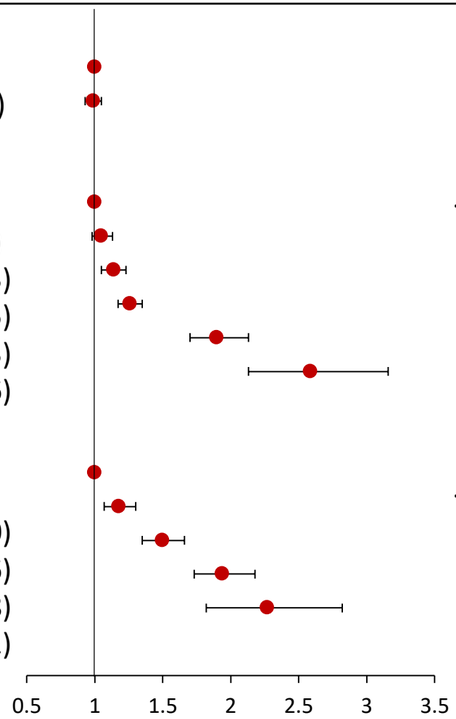
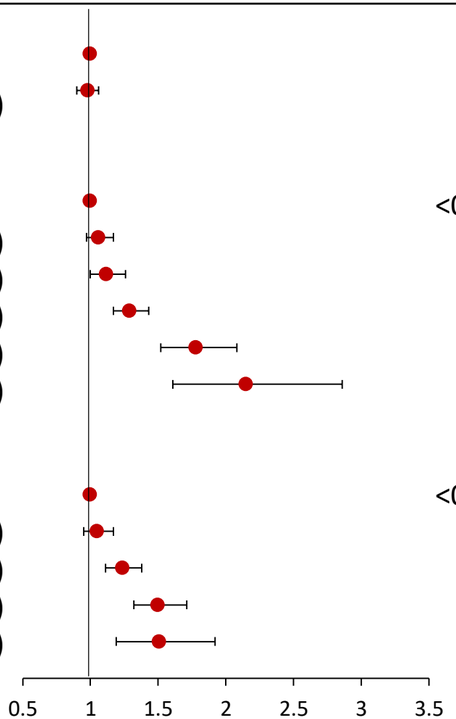


Figure 2: Patients meeting inclusion criteria



Baseline variables	Patients N=36,382	CVD events n=6,110	Risk of composite CVD (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	CVD events n=3,128	Risk of composite CVD (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	4,594	1 (reference)		16,567	2,388	1 (reference)	
Accelerated decline	9,095	1,516	0.99 (0.93 -1.05)		5,392	740	0.98 (0.90 – 1.06)	
AECOPD frequency								
None	14,450	2,175	1 (reference)	<0.001	8,957	1,134	1 (reference)	<0.001
1 moderate, 0 severe	8,509	1,375	1.05 (0.98-1.13)		5,188	715	1.06 (0.97 – 1.17)	
2 moderate, 0 severe	5,008	871	1.14 (1.05 – 1.23)		2.977	426	1.12 (1.00 – 1.26)	
3+ moderate, 0 severe	6,400	1,233	1.26 (1.17 – 1.35)		3,680	607	1.29 (1.17 – 1.43)	
1 severe, any moderate	1,582	353	1.90 (1.70 – 2.13)		926	195	1.78 (1.52 – 2.08)	
2+ severe, any moderate	433	103	2.59 (2.13 – 3.16)		231	231	2.15 (1.61 – 2.86)	
mMRC*								
0	5,003	577	1 (reference)	<0.001	4,468	525	1 (reference)	<0.001
1	9,685	1,261	1.18 (1.07 – 1.30)		8,813	1,134	1.05 (0.95 – 1.17)	
2	5,974	945	1.50 (1.35 – 1.66)		5,478	865	1.24 (1.11 – 1.38)	
3	2,980	568	1.94 (1.73 – 2.18)		2,734	519	1.50 (1.32 – 1.71)	
4	525	94	2.27 (1.82 – 2.82)		466	85	1.51 (1.19 – 1.92)	

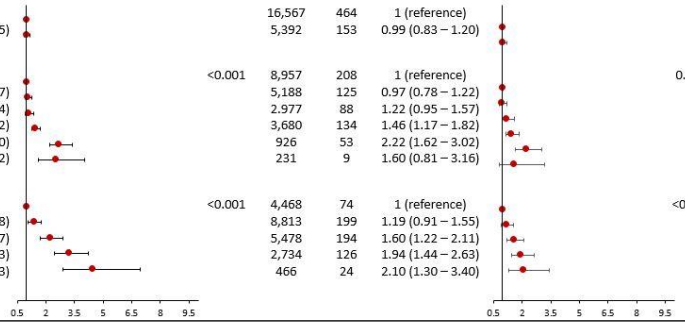




*mMRC missing in 12,215 patients

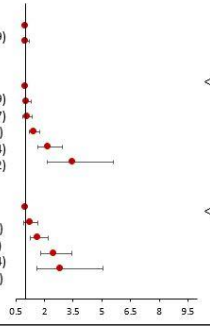
(A) Risk of heart failure

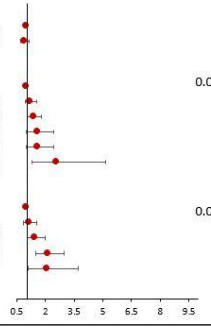
Baseline variables	Patients N=36,382	Events N=1,220	Risk of heart failure (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	Events n=617	Risk of heart failure (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	913	1 (reference)		16,567	464	1 (reference)	
Accelerated decline	9,095	307	1.01 (0.89 – 1.15)		5,392	153	0.99 (0.83 – 1.20)	
AECOPD frequency								
None	14,450	407	1 (reference)	<0.001	8,957	208	1 (reference)	0.006
1 moderate, 0 severe	8,509	268	1.09 (0.93 – 1.27)		5,188	125	0.97 (0.78 – 1.22)	
2 moderate, 0 severe	5,008	161	1.12 (0.93 – 1.34)		2.977	88	1.22 (0.95 – 1.57)	
3+ moderate, 0 severe	6,400	270	1.47 (1.26 – 1.72)		3,680	134	1.46 (1.17 – 1.82)	
1 severe, any moderate	1,582	95	2.72 (2.18 – 3.40)		926	53	2.22 (1.62 – 3.02)	
2+ severe, any moderate	433	19	2.54 (1.60 – 4.02)		231	9	1.60 (0.81 – 3.16)	
mMRC*								
0	5,003	84	1 (reference)	<0.001	4,468	74	1 (reference)	<0.001
1	9,685	218	1.39 (1.08 – 1.78)		8,813	199	1.19 (0.91 – 1.55)	
2	5,974	206	2.27 (1.73 – 2.87)		5,478	194	1.60 (1.22 – 2.11)	
3	2,980	138	3.23 (2.47 – 4.23)		2,734	126	1.94 (1.44 – 2.63)	
4	525	27	4.49 (2.91 – 6.93)		466	24	2.10 (1.30 – 3.40)	



(B) Risk of myocardial infarction

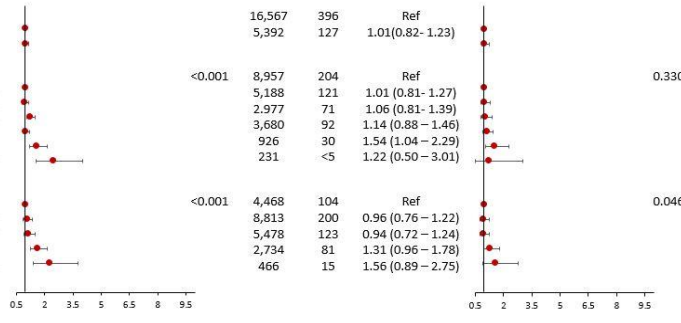
Baseline variables	Patients N=36,382	Events n=788	Risk of myocardial infarction (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	Events n=398	Risk of myocardial infarction (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	588	1 (reference)		16,567	308	1 (reference)	
Accelerated decline	9,095	200	1.02 (0.87 – 1.19)		5,392	90	0.89 (0.70 – 1.12)	
AECOPD frequency								
None	14,450	258	1 (reference)	<0.001	8,957	132	1 (reference)	0.003
1 moderate, 0 severe	8,509	173	1.07 (0.89 – 1.29)		5,188	99	1.21 (0.94 – 1.56)	
2 moderate, 0 severe	5,008	105	1.10 (0.88 – 1.37)		2.977	53	1.13 (0.83 – 1.55)	
3+ moderate, 0 severe	6,400	177	1.44 (1.20- 1.74)		3,680	81	1.38 (1.04 – 1.81)	
1 severe, any moderate	1,582	52	2.19 (1.63 – 2.94)		926	24	1.57 (1.01 – 2.45)	
2+ severe, any moderate	433	18	3.49 (2.16 – 5.62)		231	9	2.58 (1.29 – 5.16)	
mMRC*								
0	5,003	66	1 (reference)	<0.001	4,468	59	1 (reference)	0.001
1	9,685	146	1.23 (0.92- 1.63)		8,813	134	1.14 (0.85 – 1.54)	
2	5,974	120	1.65 (1.23-2.21)		5,478	111	1.45 (1.06 – 1.99)	
3	2,980	86	2.50 (1.82 – 3.44)		2,734	81	2.11(1.48 – 2.99)	
4	525	14	2.85 (1.60 -5.06)		466	13	2.07 (1.11 – 3.7)	





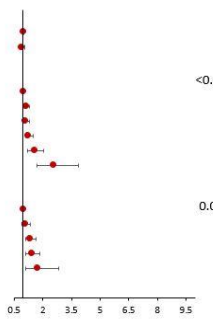
(C) Risk of stroke

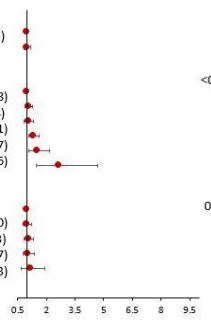
Baseline variables	Patients N=36,382	Events N=1,039	Risk of stroke (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	Events N=523	Risk of stroke (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	781	Ref		16,567	396	Ref	
Accelerated decline	9,095	258	0.99 (0.86- 1.14)		5,392	127	1.01(0.82- 1.23)	
AECOPD frequency								
None	14,450	392	Ref	<0.001	8,957	204	Ref	0.330
1 moderate, 0 severe	8,509	228	0.97 (0.82 – 1.14)		5,188	121	1.01 (0.81- 1.27)	
2 moderate, 0 severe	5,008	170	1.23 (1.03 – 1.47)		2.977	71	1.06 (0.81- 1.39)	
3+ moderate, 0 severe	6,400	178	1.00 (0.84 – 1.20)		3,680	92	1.14 (0.88 – 1.46)	
1 severe, any moderate	1,582	53	1.58 (1.19 -2.11)		926	30	1.54 (1.04 – 2.29)	
2+ severe, any moderate	433	18	2.50 (1.56 – 4.01)		231	<5	1.22 (0.50 – 3.01)	
mMRC*								
0	5,003	111	Ref	<0.001	4,468	104	Ref	0.046
1	9,685	224	1.09 (0.87 – 1.36)		8,813	200	0.96 (0.76 – 1.22)	
2	5,974	141	1.17 (0.91 – 1.49)		5,478	123	0.94 (0.72 – 1.24)	
3	2,980	91	1.62 (1.23 -2.14)		2,734	81	1.31 (0.96 – 1.78)	
4	525	18	2.27 (1.38 – 3.74)		466	15	1.56 (0.89 – 2.75)	



(D) Risk of atrial fibrillation

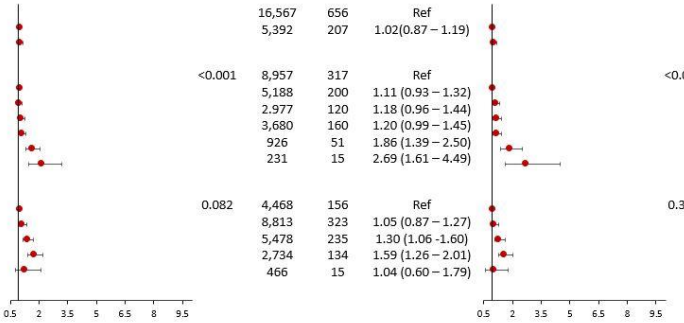
Baseline variables	Patients N=36,382	Events n=1,427	Risk of atrial fibrillation (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	Events n=727	Risk of atrial fibrillation (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	1,092	1 (reference)		16,567	564	1 (reference)	
Accelerated decline	9,095	335	0.92(0.82-1.04)		5,392	163	0.97 (0.81 -1.15)	
AECOPD frequency								
None	14,450	508	1 (reference)	<0.001	8,957	273	1 (reference)	<0.001
1 moderate, 0 severe	8,509	346	1.14 (0.99 – 1.30)		5,188	170	1.06 (0.87 – 1.28)	
2 moderate, 0 severe	5,008	199	1.12 (0.95 – 1.32)		2.977	94	1.06 (0.83- 1.34)	
3+ moderate, 0 severe	6,400	288	1.27 (1.10-1.47)		3,680	140	1.31 (1.07 – 1.61)	
1 severe, any moderate	1,582	67	1.57 (1.22 – 2.03)		926	37	1.53 (1.07 – 2.17)	
2+ severe, any moderate	433	23	2.56 (1.68- 3.88)		231	13	2.64 (1.49 – 4.66)	
mMRC*								
0	5,003	154	1 (reference)	0.006	4,468	132	1 (reference)	0.524
1	9,685	317	1.11 (0.91 -1.34)		8,813	278	0.98 (0.79 – 1.20)	
2	5,974	227	1.36 (1.11 – 1.66)		5,478	202	1.06(0.85 – 1.33)	
3	2,980	110	1.43 (1.12 – 1.82)		2,734	97	1.03 (0.78 – 1.37)	
4	525	19	1.75 (1.09 – 2.82)		466	18	1.16 (0.69 – 1.93)	





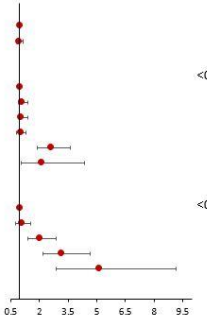
(E) Risk of coronary artery disease

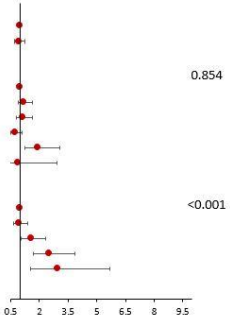
Baseline variables	Patients N=36,382	Events N=1,636	Risk of coronary artery disease (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	Events n=863	Risk of coronary artery disease (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	1,220	Ref		16,567	656	Ref	
Accelerated decline	9,095	416	1.03(0.93-1.15)		5,392	207	1.02(0.87 – 1.19)	
AECOPD frequency								
None	14,450	610	Ref	<0.001	8,957	317	Ref	<0.001
1 moderate, 0 severe	8,509	355	0.98 (0.87 – 1.12)		5,188	200	1.11 (0.93 – 1.32)	
2 moderate, 0 severe	5,008	236	1.09 (0.94- 1.26)		2.977	120	1.18 (0.96 – 1.44)	
3+ moderate, 0 severe	6,400	324	1.14 (1.00 – 1.31)		3,680	160	1.20 (0.99 – 1.45)	
1 severe, any moderate	1,582	86	1.64 (1.32 -2.04)		926	51	1.86 (1.39 – 2.50)	
2+ severe, any moderate	433	25	2.17 (1.46 - 3.21)		231	15	2.69 (1.61 – 4.49)	
mMRC*								
0	5,003	162	Ref	0.082	4,468	156	Ref	0.317
1	9,685	356	1.14 (0.95 – 1.37)		8,813	323	1.05 (0.87 – 1.27)	
2	5,974	251	1.43 (1.18 – 1.73)		5,478	235	1.30 (1.06 -1.60)	
3	2,980	143	1.77 (1.43 – 2.20)		2,734	134	1.59 (1.26 – 2.01)	
4	525	16	1.26 (0.75 – 2.10)		466	15	1.04 (0.60 – 1.79)	



(F) Risk of CVD mortality

Baseline variables	Patients N=36,382	Events N=556	Risk of CVD mortality (unadjusted HR, 95% CI)	P for trend	Patients N=21,959	Events n=282	Risk of CVD mortality (adjusted HR, 95% CI)	P for trend
FEV_1 decline								
Non-accelerated decline	27,287	421	Ref		16,567	215	Ref	
Accelerated decline	9,095	125	0.96 (0.79-1.17)		5,392	67	0.94 (0.71-1.25)	
AECOPD frequency								
None	14,450	200	Ref	<0.001	8,957	105	Ref	0.854
1 moderate, 0 severe	8,509	135	1.12 (0.90-1.39)		5,188	75	1.19 (0.89-1.61)	
2 moderate, 0 severe	5,008	75	1.06 (0.90-1.38)		2.977	40	1.13 (0.78-1.63)	
3+ moderate, 0 severe	6,400	93	1.03 (0.81-1.31)		3,680	34	0.73 (0.5-1.09)	
1 severe, any moderate	1,582	45	2.61 (1.90-3.61)		926	25	1.94 (1.24-3.05)	
2+ severe, any moderate	433	8	2.13 (1.05-4.34)		231	<3	0.91 (0.29-2.92)	
mMRC*								
0	5,003	43	Ref	<0.001	4,468	39	Ref	<0.001
1	9,685	86	1.08 (0.75-1.55)		8,813	77	0.94 (0.64-1.39)	
2	5,974	95	2.02 (1.41-2.89)		5,478	85	1.57 (1.06-2.32)	
3	2,980	69	3.16 (2.16-4.63)		2,734	68	2.52 (1.66-3.83)	
4	525	16	5.15 (2.90-9.16)		466	13	2.94 (1.52-2.94)	





*mMRC missing in proportion of patients under "unadjusted" analyses. See table 1 for further information

Accelerated FEV_1 decline and risk of cardiovascular disease and mortality in a primary care population of COPD patients

Supplementary material

Contents

Table E1: Relationship between accelerated FEV1 decline and risk of composite CVD

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	0.99 (0.93 – 1.05)	0.98 (0.90 – 1.06)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.05 (0.98 – 1.13)	1.06 (0.97 – 1.17)
2 moderate, 0 severe	1.14 (1.05 – 1.23)*	1.12 (1.00 – 1.26)*
≥3 moderate, 0 severe	1.26 (1.17 – 1.35)**	1.29 (1.17 – 1.43)**
1 severe, any moderate	1.90 (1.70 – 2.13)**	1.78 (1.52 – 2.08)**
≥2 severe, any moderate	2.59 (2.13 – 3.16)**	2.15 (1.61 – 2.86)**
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.05 (0.98 – 1.12)	1.06 (0.96 – 1.16)
30-50%	1.15 (1.07 – 1.24)**	1.02 (0.92 – 1.14)
<30%	1.23 (1.10 – 1.38)**	1.10 (0.93 – 1.30)
Age	1.05 (1.04 – 1.05)**	1.04 (1.04 – 1.05)**
Men	1.33 (1.27 – 1.40)**	1.40 (1.29 – 1.51)**
Current smokers	0.83 (0.78 – 0.87)**	1.13 (1.05 – 1.22)*
BMI		
Normal	Ref	Ref
Underweight	1.04 (0.91 – 1.20)	1.08 (0.89 – 1.30)
Overweight	1.10 (1.03 – 1.18)*	1.01 (0.93 – 1.10)
Obese	1.11 (1.04 – 1.19)**	1.09 (0.99 – 1.19)
mMRC		
0	Ref	Ref
1	1.18 (1.07 – 1.30)*	1.05 (0.95 – 1.17)
2	1.50 (1.35 – 1.66)**	1.24 (1.11 – 1.38)**
3	1.94 (1.73 – 2.18)**	1.50 (1.32 – 1.71)**
4	2.27 (1.82 – 2.82)**	1.51 (1.19 – 1.92)*
Asthma	0.91 (0.87 – 0.96)**	1.02 (0.95 – 1.10)
Hypertension	1.66 (1.58 – 1.74)**	1.31 (1.21 – 1.41)**
Diabetes	1.39 (1.30 – 1.50)**	1.09 (0.99 – 1.21)
Statin use	1.40 (1.33 – 1.47)**	1.14 (1.05 – 1.23)*

*p value <0.05; **p value<0.0001

Table E2: Relationship between accelerated FEV1 decline and risk of heart failure

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	1.01 (0.89 – 1.15)	0.99 (0.83 – 1.20)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.09 (0.93 – 1.27)	0.97 (0.78 – 1.22)
2 moderate, 0 severe	1.12 (0.93 – 1.34)	1.22 (0.95 – 1.57)
≥3 moderate, 0 severe	1.47 (1.26 – 1.72)**	1.46 (1.17 – 1.82)*
1 severe, any moderate	2.72 (2.18 – 3.40)**	2.22 (1.62 – 3.02)**
≥2 severe, any moderate	2.54 (1.60 – 4.02)**	1.60 (0.81 – 3.16)
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.18 (1.00 – 1.39)*	1.21 (0.97 – 1.52)
30-50%	1.74 (1.48 – 2.06)**	1.55 (1.21 – 1.98)*
<30%	2.07 (1.64 – 2.62)**	1.91 (1.34 – 2.70)**
Age	1.06 (1.05 – 1.07)**	1.10 (1.05 – 1.07)**
Men	1.23 (1.10 – 1.38)**	1.61 (1.36 – 1.91)**
Current smokers	0.79 (0.70 – 0.88)**	1.15 (0.97 – 1.36)
BMI		
Normal	Ref	Ref
Underweight	1.27 (0.94 – 1.70)	1.19 (0.80 – 1.78)
Overweight	1.02 (0.87 – 1.18)	0.89 (0.72 – 1.09)
Obese	1.35 (1.16 – 1.56)**	1.31 (1.07 – 1.62)*
mMRC		
0	Ref	Ref
1	1.39 (1.08 – 1.78)*	1.19 (0.91 – 1.55)
2	2.27 (1.73 – 2.87)**	1.60 (1.22 – 2.11)*
3	3.23 (2.47 – 4.23)**	1.94 (1.44 – 2.63)**
4	4.49 (2.91 – 6.93)**	2.10 (1.30 – 3.40)*
Asthma	0.85 (0.76 – 0.95)*	0.88 (0.74 – 1.04)
Hypertension	2.30 (2.05 – 2.58)**	1.70 (1.42 – 2.03)**
Diabetes	1.78 (1.54 – 2.07)**	1.25 (1.00-1.56)*
Statin use	1.43 (1.27 – 1.60)**	0.97 (0.81 – 1.16)

*p value <0.05; **p value<0.0001

Table E3: Relationship between accelerated FEV1 decline and risk of myocardial infarction

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	1.02 (0.87 – 1.19)	0.89 (0.70 – 1.12)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.07 (0.89 – 1.29)	1.21 (0.94 – 1.56)
2 moderate, 0 severe	1.10 (0.88 – 1.37)	1.13 (0.83 – 1.55)
≥3 moderate, 0 severe	1.44 (1.20- 1.74)**	1.38 (1.04 – 1.81)*
1 severe, any moderate	2.19 (1.63 – 2.94)**	1.57 (1.01 – 2.45)*
≥2 severe, any moderate	3.49 (2.16 – 5.62)**	2.58 (1.29 – 5.16)*
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.01 (0.84 – 1.21)	1.08 (0.83 – 1.40)
30-50%	1.30 (1.08 – 1.58)*	1.18 (0.88 – 1.59)
<30%	1.31 (0.97 – 1.78)	1.08 (0.68 – 1.72)
Age	1.04(1.03 – 1.04)**	0.14 (2.03 -1.05)**
Men	1.50 (1.31 -1.72)**	1.44(1.17 – 1.77)*
Current smokers	1.09(0.95 – 1.26)	1.45 (1.17 – 1.81)*
BMI		
Normal	Ref	Ref
Underweight	1.36 (0.98 – 1.88)	1.43 (0.94 – 2.17)
Overweight	0.97 (0.82 – 1.16)	0.87 (0.69 – 1.10)
Obese	0.76 (0.63 – 0.93)*	0.69 (0.53- 0.91)*
mMRC		
0	Ref	Ref
1	1.23 (0.92- 1.63)	1.14 (0.85 – 1.54)
2	1.65 (1.23-2.21)*	1.45 (1.06 – 1.99)*
3	2.50 (1.82 – 3.44)**	2.11(1.48 – 2.99)**
4	2.85 (1.60 -5.06)**	2.07 (1.11 – 3.7)*
Asthma	0.90 (0.79 – 1.03)	1.07 (0.88 – 1.31)
Hypertension	1.21 (1.06 – 1.39)*	1.08 (0.88 – 1.34)
Diabetes	1.30 (1.06 – 1.60)*	1.03(1.11 – 3.87)*
Statin use	1.01 (0.87 – 1.17)	1.16 (0.93 -1.44)

*p value <0.05; **p value<0.0001

Table E4: Relationship between accelerated FEV1 decline and risk of stroke

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	0.99 (0.86- 1.14)	1.01(0.82- 1.23)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	0.97 (0.82 – 1.14)	1.01 (0.81- 1.27)
2 moderate, 0 severe	1.23 (1.03 – 1.47)*	1.06 (0.81- 1.39)
≥3 moderate, 0 severe	1.00 (0.84 – 1.20)	1.14 (0.88 – 1.46)
1 severe, any moderate	1.58 (1.19 -2.11)*	1.54 (1.04 – 2.29)*
≥2 severe, any moderate	2.50 (1.56 – 4.01)**	1.22 (0.50 – 3.01)
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.16 (0.99 – 1.36)	1.20 (0.95 – 1.50)
30-50%	1.07 (0.90 – 1.28)	1.03 (0.79 – 1.36)
<30%	1.28 (0.97 – 1.68)	1.26 (0.83-1.91)
Age	1.06 (1.05 – 1.06)**	1.05 (1.04 – 1.06)**
Men	1.24 (1.10 – 1.40)*	1.29 (1.07 – 1.55)*
Current smokers	0.87 (0.77 – 0.98)*	1.24 (1.03 – 1.50)*
BMI		
Normal	Ref	Ref
Underweight	0.83 (0.59 – 1.17)	0.85 (0.54 – 1.35)
Overweight	0.97 (0.83-1.12)	0.97 (0.80 – 1.18)
Obese	0.63 (0.53 – 0.76)**	0.65 (0.51-0.84)*
mMRC		
0	Ref	Ref
1	1.09 (0.87 – 1.36)	0.96 (0.76 – 1.22)
2	1.17 (0.91 – 1.49)	0.94 (0.72 – 1.24)
3	1.62 (1.23 -2.14)*	1.31 (0.96 – 1.78)
4	2.27 (1.38 – 3.74)*	1.56 (0.89 – 2.75)
Asthma	0.77 (0.68 – 0.87)**	0.82(0.68 – 0.99)*
Hypertension	1.37 (1.22 – 1.55)**	1.00 (0.83 – 1.21)
Diabetes	1.23 (1.03 – 1.48)*	1.23 (0.94-1.61)
Statin use	2.30 (1.14 – 1.47)**	0.97 (0.80 – 1.19)

*p value <0.05; **p value<0.0001

Table E5: Relationship between accelerated FEV1 decline and risk of atrial fibrillation

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	0.92(0.82-1.04)	0.97 (0.81 -1.15)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.14 (0.99 – 1.30)	1.06 (0.87 – 1.28)
2 moderate, 0 severe	1.12 (0.95 – 1.32)	1.06 (0.83- 1.34)
≥3 moderate, 0 severe	1.27 (1.10-1.47)*	1.31 (1.07 – 1.61)*
1 severe, any moderate	1.57 (1.22 – 2.03)*	1.53 (1.07 – 2.17)*
≥2 severe, any moderate	2.56 (1.68- 3.88)**	2.64 (1.49 – 4.66)*
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.11 (0.97 – 1.28)	1.06 (0.88 – 1.28)
30-50%	1.26 (1.09-1.46)*	1.09(0.87 – 1.36)
<30%	1.20(0.94 – 1.53)	1.09 (0.75 -1.60)
Age	1.07 (1.06 – 1.07)**	1.07 (1.06 – 1.-8)**
Men	1.39 (1.25 – 1.54)**	1.44 (1.23- 1.68)**
Current smokers	0.61 (0.55 – 0.68)**	0.91 (0.78 – 1.06)
BMI		
Normal	Ref	Ref
Underweight	0.95 (0.69 -1.32)	1.28 (0.84 – 1.93)
Overweight	1.29 (1.12-1.48)**	1.26 (1.05- 1.52)*
Obese	1.37 (1.18 – 1.58)**	1.50 (1.23 – 1.83)**
mMRC		
0	Ref	Ref
1	1.11 (0.91 -1.34)	0.98 (0.79 – 1.20)
2	1.36 (1.11 – 1.66)*	1.06(0.85 – 1.33)
3	1.43 (1.12 – 1.82)*	1.03 (0.78 – 1.37)
4	1.75 (1.09 – 2.82)*	1.16 (0.69 – 1.93)
Asthma	0.01 (0.82-1.01)	1.09 (0.94-1.27)
Hypertension	1.82 (1.64 – 2.12)**	1.42 (1.21- 1.67)**
Diabetes	1.25 (1.07 -1.46)*	1.09 (0.88 – 1.35)
Statin use	1.25 (1.12- 1.40)**	0.99 (0.84-1.16)

*p value <0.05; **p value<0.0001

Table E6: Relationship between accelerated FEV1 decline and risk of coronary artery disease excluding myocardial infarction

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	1.03(0.93-1.15)	1.02(0.87 – 1.19)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	0.98 (0.87 – 1.12)	1.11 (0.93 – 1.32)
2 moderate, 0 severe	1.09 (0.94- 1.26)	1.18 (0.96 – 1.44)
≥3 moderate, 0 severe	1.14 (1.00 – 1.31)*	1.20 (0.99 – 1.45)
1 severe, any moderate	1.64 (1.32 -2.04)**	1.86 (1.39 – 2.50)**
≥2 severe, any moderate	2.17 (1.46 - 3.21)**	2.69 (1.61 – 4.49)**
FEV1 % predicted		
>80%	Ref	Ref
50-80%	0.90 (0.80 – 1.01)	0.91 (0.77 – 1.07)
30-50%	0.77 (0.68 – 0.89)**	0.68 (0.56 – 0.84)**
<30%	0.82 (0.66 – 1.03)	0.70 (0.50- 0.99)*
Age	1.02 (1.02 -1.02)**	1.02 (0.87 – 1.19)
Men	1.28 (1.25 -1.52)**	1.33 (1.15 – 1.53)*
Current smokers	0.97 (0.88- 1.07)	1.31 (1.04 -1.39)*
BMI		
Normal	Ref	Ref
Underweight	0.94 (0.71 -1.25)	0.74 (0.47 – 1.16)
Overweight	1.17 (1.03-1.33)*	1.02 (0.87 – 1.20)
Obese	1.27 (1.12- 1.45)**	1.13 (0.95 – 1.35)
mMRC		Ref
0	Ref	1.05 (0.87 – 1.27)
1	1.14 (0.95 – 1.37)	1.30 (1.06 -1.60)*
2	1.43 (1.18 – 1.73)**	1.59 (1.26 – 2.01)**
3	1.77 (1.43 – 2.20)**	1.04 (0.60 – 1.79)
4	1.26 (0.75 – 2.10)	
Asthma	1.07 (0.97 – 1.18)	1.17(1.03 -1.34)*
Hypertension	1.61 (1.46 – 1.77)**	1.32 (1.14 – 1.53)**
Diabetes	1.42 (1.24 – 1.63)**	0.94 (0.78 – 1.15)
Statin use	1.80 (1.64 – 1.99)**	1.60 (1.39 – 1.85)**

*p value <0.05; **p value<0.0001

Table E7: Relationship between accelerated FEV1 decline and risk of CVD death

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV_1 decline	0.96 (0.79-1.17)	0.94 (0.71-1.25)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.12 (0.90-1.39)	1.19 (0.89-1.61)
2 moderate, 0 severe	1.06 (0.90-1.38)	1.13 (0.78-1.63)
≥3 moderate, 0 severe	1.03 (0.81-1.31)	0.73 (0.50-1.09)
1 severe, any moderate	2.61 (0.80-1.61)**	1.94 (1.24-3.05)*
≥2 severe, any moderate	2.13 (1.90-4.34)*	0.91 (0.29-2.92)
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.23 (0.97-1.57)	1.12 (0.81-1.54)
30-50%	1.87 (1.46-2.40)**	1.23 (0.86-1.77)
<30%	2.18 (1.53-3.09)**	1.40 (0.83-2.38)
Age	1.06 (1.05-1.08)**	1.06 (1.04-1.07)**
Men	1.50 (1.26-1.78)**	1.80 (1.40-2.32)**
Current smokers	1.08 (0.91-1.29)	1.62 (1.24-2.10)**
BMI		
Normal	Ref	Ref
Underweight	1.28 (0.87-1.89)	1.03 (0.59-1.81)
Overweight	0.73 (0.59-0.92)*	0.63 (0.47-0.86)*
Obese	0.84 (0.67-1.06)	0.94 (0.70-1.27)
mMRC		
0	Ref	Ref
1	1.08 (0.75-1.55)	0.94 (0.64-1.39)
2	2.02 (1.41-2.89)	1.57 (1.06-2.32)*
3	3.16 (2.16-4.63)	2.52 (1.66-3.83)**
4	5.15 (2.90-9.16)	2.94 (1.52-5.69)*
Asthma	0.78 (0.66-0.93)*	0.80 (0.62-1.03)
Hypertension	1.83 (1.55-2.16)**	1.49 (1.15-1.93)*
Diabetes	1.62 (1.29-2.04)**	0.90 (0.63-1.29)
Statin use	1.27 (1.-7-1.51)*	1.17 (0.90-1.52)

*p value <0.05; **p value<0.0001

Table E8: Relationship between risk of CVD outcomes and accelerated FEV_1 decline (by quartiles, measured relative to baseline, measured as percent predicted, and linearly)

Model	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Quartile 1 (slowest decline)	Ref	Ref
Quartile 2	1.05 (0.98 – 1.13)	0.96 (0.87 – 1.06)
Quartile 3	1.06 (0.98 – 1.14)	0.96 (0.87 – 1.06)
Quartile 4 (accelerated decline)	1.02 (0.95– 1.10)	0.95 (0.85 – 1.05)
Decline in relative FEV_1	1.06 (1.00 – 1.13)	1.00 (0.91 – 1.09)
Decline in FEV_1 % predicted	1.05 (0.98 – 1.13)	1.00 (0.90 – 1.11)
Linear FEV_1 decline	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)

*p value <0.05; **p value<0.0001

Table E9: Relationship between rate of FEV1 decline and risk of composite CVD

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Decline		
>-20ml/year	Ref	Ref
-20 to -40 ml/year	1.05 (0.99 – 1.12)	1.00 (0.91 - 1.09)
-40 to -60ml/year	0.98(0.91 – 1.07)	0.91 (0.81-1.02)
<-60ml	1.01 (0.93 – 1.09)	1.02 (0.91 – 1.14)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.05 (0.98 – 1.13)	1.06 (0.97 – 1.17)
2 moderate, 0 severe	1.14 (1.05 – 1.23)*	1.12 (1.00 – 1.26)*
≥3 moderate, 0 severe	1.26 (1.17 – 1.35)**	1.29 (1.17 – 1.43)**
1 severe, any moderate	1.90 (1.70 – 2.13)**	1.78 (1.52 – 2.08)**
≥2 severe, any moderate	2.59 (2.13 – 3.16)**	2.15 (1.61 – 2.86)**
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.05 (0.98 – 1.12)	1.06 (0.96 – 1.16)
30-50%	1.15 (1.07 – 1.24)**	1.02 (0.92 – 1.14)
<30%	1.23 (1.10 – 1.38)**	1.10 (0.92 – 1.30)
Age	1.05 (1.04 – 1.05)**	1.04 (1.04 – 1.05)**
Men	1.33 (1.27 – 1.40)**	1.39 (1.29 – 1.50)**
Current smokers	0.83 (0.78 – 0.87)**	1.13 (1.05 – 1.22)*
BMI		
Normal	Ref	Ref
Underweight	1.04 (0.91 – 1.20)	1.08 (0.89 – 1.30)
Overweight	1.10 (1.03 – 1.18)*	1.01 (0.93 – 1.10)
Obese	1.11 (1.04 – 1.19)**	1.08 (0.99 – 1.19)
mMRC		
0	Ref	Ref
1	1.18 (1.07 – 1.30)*	1.05 (0.95 – 1.17)
2	1.50 (1.35 – 1.66)**	1.24 (1.10 – 1.38)**
3	1.94 (1.73 – 2.18)**	1.50 (1.32 – 1.71)**
4	2.27 (1.82 – 2.82)**	1.52 (1.19 – 1.92)*
Asthma	0.91 (0.87 – 0.96)**	1.02 (0.95 – 1.10)
Hypertension	1.66 (1.58 – 1.74)**	1.31 (1.21 – 1.41)**
Diabetes	1.39 (1.30 – 1.50)**	1.09 (0.99 – 1.21)
Statin use	1.40 (1.33 – 1.47)**	1.14 (1.05 – 1.23)*

*p value <0.05; **p value<0.0001

Table E10: Relationship between accelerated FEV_1 decline and risk of composite CVD in patients without a history of asthma

Model	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Accelerated FEV1 decline	0.98 (0.90 – 1.07)	0.96 (0.85 – 1.08)

*p value <0.05; **p value<0.0001

Table E11: Relationship between accelerated FEV1 decline and risk of GP diagnosed CVD, hospitalised CVD, and death from CVD

Model	Crude HR (95% CI)	Adjusted HR (95% CI)
GP diagnosed CVD	0.96 (0.89 – 1.04)	0.93 (0.83 – 1.05)
Hospitalised CVD	1.02 (0.90 – 1.16)	0.96 (0.79 – 1.16)
Death from CVD	0.96 (0.70 – 1.17)	0.94 (0.71 – 1.25)

*p value <0.05; **p value<0.0001

Table E12: Relationship between accelerated FEV1 decline and risk of composite CVD stratified by gender, age, smoking status, AECOPD, mMRC, and airflow obstruction

Model	Crude HR (95% CI)	Adjusted HR (95% CI)
Males	0.93 (0.85 – 1.03)	0.98 (0.85 – 1.12)
Females	0.97 (0.90 – 1.04)	0.98 (0.88– 1.09)
Stratified by age		
35-50	0.92 (0.62 – 1.38)	0.58 (0.30 – 1.12)
50-65	1.07 (0.95 – 1.20)	1.02 (0.86 – 1.21)
65-80	1.04 (0.96 – 1.13)	0.91 (0.81 – 1.02)
80≤	1.15 (1.00 – 1.32)	1.11 (0.92 – 1.35)
Stratified by smoking status		
Ex-smoker	0.94 (0.86 – 1.03)	0.93 (0.81 – 1.07)
Current smoker	1.03 (0.96 – 1.11)	1.00 (0.89 – 1.11)
Stratified by AECOPD		
0, 1, or 2 mod & no severe	0.98 (0.92 – 1.05)	0.98 (0.89 – 1.09)
3 mod & no severe or any severe	0.98 (0.88 – 1.09)	0.99 (0.84 – 1.16)
Stratified by mMRC		
0	1.05 (0.86 – 1.27)	1.02 (0.82 – 1.26)
1	1.00 (0.88 – 1.14)	0.98 (0.85 – 1.12)
2	0.94 (0.81 – 1.09)	0.99 (0.84 – 1.16
3	0.89 (0.73 – 1.08)	0.95 (0.77 – 1.17)
4	0.73 (0.46 – 1.16)	0.73 (0.44 – 1.21)
Stratified by airflow obstruction		
≥80% FEV_1 predicted		
50-80% FEV_1 predicted	1.01 (0.88 - 1.16)	0.97 (0.83 – 1.12)
30-50% FEV_1 predicted	0.99 (0.90 – 1.08)	1.02 (0.93 – 1.13)
≤30% FEV_1 predicted	0.92 (0.83 – 1.02)	0.99 (0.88 – 1.11)
	1.02 (0.83– 1.26)	1.08 (0.86 – 1.36)

*p value <0.05; **p value<0.0001

Table E13: Relationship between accelerated FEV1 decline and risk of composite CVD in patients with at least 4 FEV1 measurements during baseline period

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV1 decline	1.02 (0.92 – 1.14)	1.04 (0.90 – 1.21)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.11 (0.97 – 1.27)	1.17 (0.98 – 1.40)
2 moderate, 0 severe	1.20 (1.03 – 1.40)*	1.22 (0.99 – 1.50)
≥3 moderate, 0 severe	1.33 (1.17 – 1.51)**	1.46 (1.22 – 1.76)**
1 severe, any moderate	2.12 (1.75 – 2.58)**	2.07 (1.59 – 2.69)**
≥2 severe, any moderate	2.41 (1.72 – 3.39)**	2.17 (1.33 – 3.53)*
FEV1 % predicted		
>80%	Ref	Ref
50-80%	1.00 (0.88 – 1.14)	1.09 (0.92 – 1.30)
30-50%	1.09 (0.95 – 1.25)	1.39 (0.85 – 1.28)
<30%	1.00 (0.81 – 1.24)	1.02 (0.74 – 1.41)
Age	1.05 (1.04 – 1.05)**	1.05 (1.04 – 1.05)**
Men	1.51 (1.37 – 1.67)**	1.65 (1.43 – 1.90)**
Current smokers	0.85 (0.77 – 0.93)*	1.23 (1.07 -1.42)*
BMI		
Normal	Ref	Ref
Underweight	0.80 (0.60 – 1.07)	0.91 (0.62 – 1.32)
Overweight	1.01 (0.90 – 1.14)	0.88 (0.75 – 1.03)
Obese	1.01 (0.88 – 1.15)	0.97 (0.81 – 1.15)
mMRC		
0	Ref	Ref
1	1.14 (0.94 – 1.38)	1.03 (0.84 – 1.26)
2	1.55 (1.27 – 1.88)**	1.28 (1.03 – 1.58)*
3	1.84 (1.48 – 2.29)**	1.49 (1.18 – 1.89)*
4	2.35 (1.58 – 3.50)**	1.50 (0.97 – 2.31)
Asthma	0.90 (0.81 – 0.99)*	1.01 (0.89 – 1.16)
Hypertension	1.64 (1.49 – 1.81)**	1.41 (1.22 – 1.62)**
Diabetes	1.40 (1.21 – 1.61)**	1.19 (0.99 – 1.44)
Statin use	1.39 (1.26 – 1.53)**	1.02 (0.88 – 1.18)

*p value <0.05; **p value<0.0001

Table E14: Relationship between accelerated FEV1 decline and risk of composite CVD in patients with at least 2 FEV1 measurements at least 2 years apart.

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
Accelerated FEV1 decline	1.07 (0.95 – 1.20)	0.95 (0.79 – 1.14)
AECOPD		
None	Ref	Ref
1 moderate, 0 severe	1.05 (0.98 – 1.13)	0.95 (0.78 – 1.15)
2 moderate, 0 severe	1.14 (1.05 – 1.23)*	0.96 (0.75 – 1.22)
≥3 moderate, 0 severe	1.26 (1.17 – 1.35)**	1.13 (0.91 – 1.39)
1 severe, any moderate	1.90 (1.70 – 2.13)**	1.54 (1.11 -2.14)*
≥2 severe, any moderate	2.59 (2.13 – 3.16)**	1.63 (0.83 – 3.20)
FEV1 % predicted		Ref
>80%	Ref	0.94 (0.77 – 1.15)
50-80%	1.05 (0.98 – 1.12)	1.14 (0.91 – 1.43)
30-50%	1.15 (1.07 – 1.24)**	1.33 (0.95 – 1.86)
<30%	1.23 (1.10 – 1.38)**	
Age	1.05 (1.-4 – 1.05)**	1.04(1.02 – 1.05)**
Men	1.33 (1.27 – 140)**	1.32 (1.12 – 1.55)*
Current smokers	0.82 (0.78 – 0.87)**	1.07 (0.91 – 1.26)
BMI		Ref
Normal	Ref	1.19 (0.79 – 1.77)
Underweight	1.04 (0.91 – 1.20)	1.23 (1.02 – 1.48)*
Overweight	1.10 (1.03 – 1.18)*	1.11 (0.90 – 1.37)
Obese	1.11 (1.04 – 1.19)*	
mMRC		
0	Ref	Ref
1	1.18 (1.07 – 1.30)*	1.13 (0.90 – 1.41)
2	1.50 (1.35 – 1.66)**	1.39 (1.10 – 1.76)*
3	1.94 (1.72 – 2.18)**	1.52 (1.15 – 2.01)*
4	2.27 (1.82 – 2.82)**	1.76 (1.08 – 2.85)*
Asthma	0.92 (0.87 – 0.96)**	1.01 (0.86 – 1.18)
Hypertension	1.66 (1.58 – 1.74)**	1.34 (1.14 – 1.59)**
Diabetes	1.39 (1.30 – 1.50)**	1.06 (0.85 – 1.34)
Statin use	1.40 (1.33 – 1.47)**	1.29 (1.09 – 1.53)*

*p value <0.05; **p value<0.0001

Figure E1: Number of FEV_1 measurements over the three-year baseline period (N=36,382)

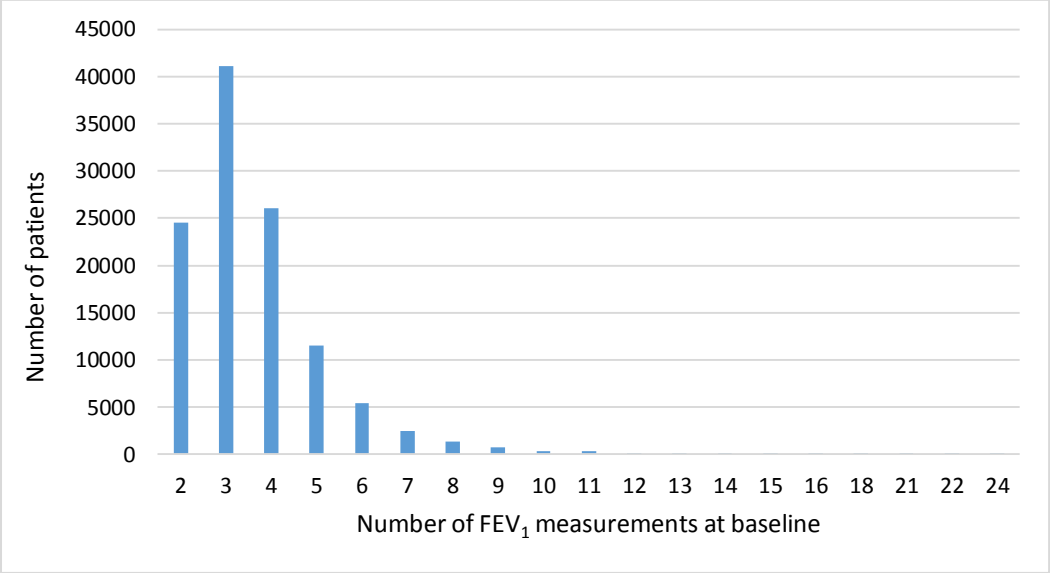


Figure E2: Time intervals between FEV_1 measurements over the three-year baseline period

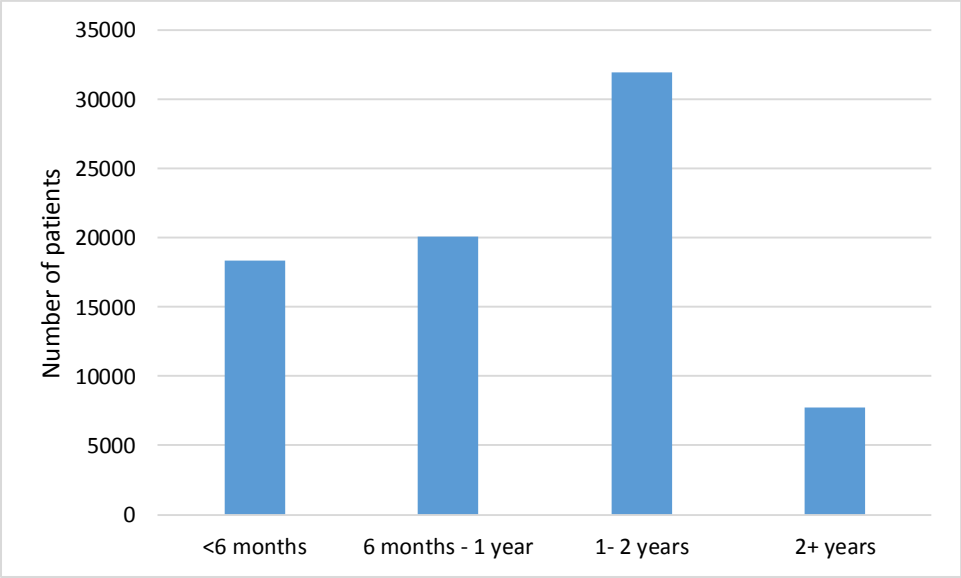


Figure E3: Spline regression with knots at the 10th, 50th, and 90th percentile

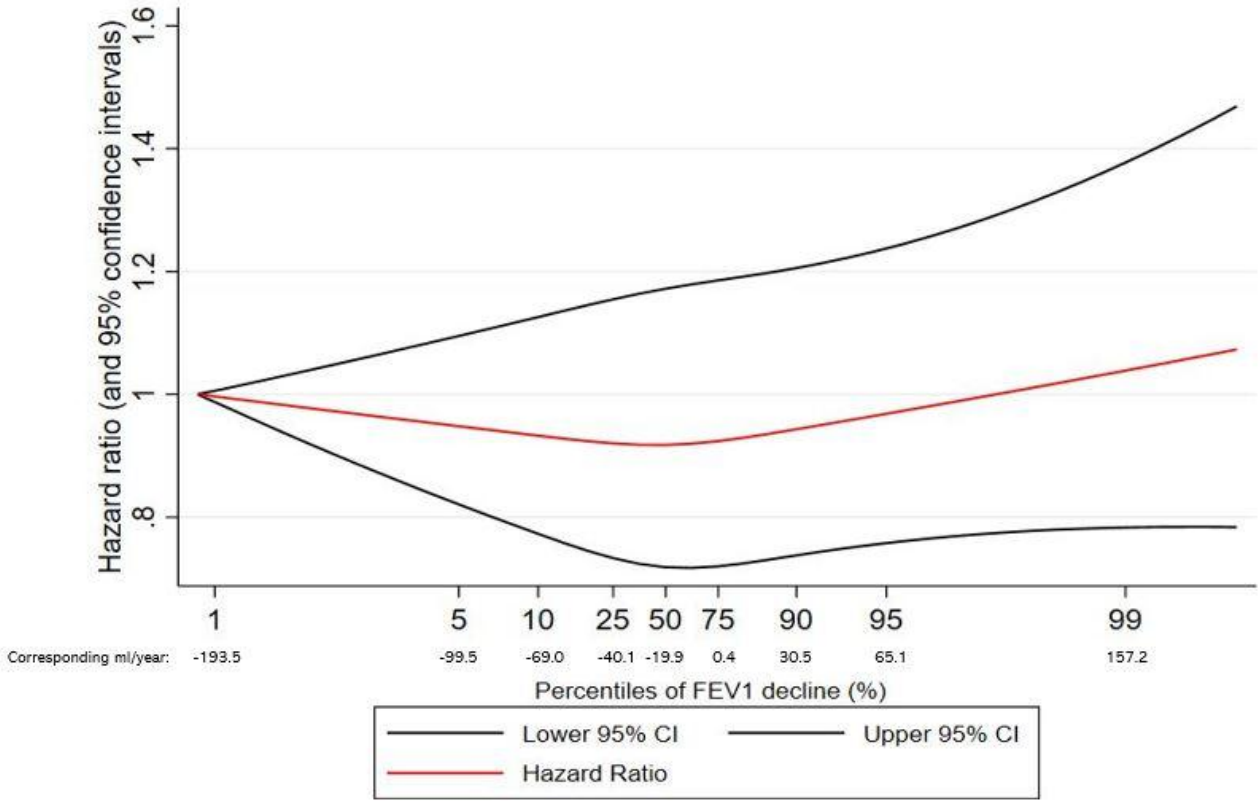


Figure E4: Association between composite CVD, heart failure, myocardial infarction, stroke, atrial fibrillation, and coronary artery disease and angina and accelerated FEV_1 decline compared to non-accelerated FEV_1 decline in the first year of follow-up.

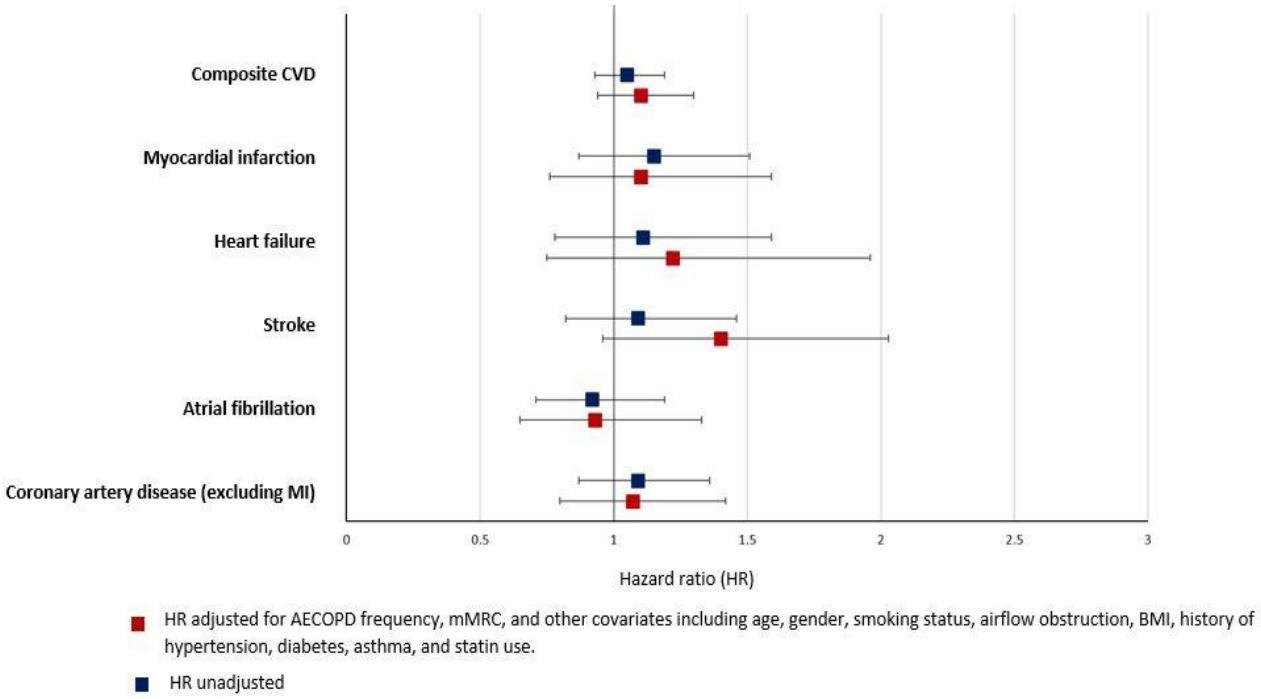


Figure E5: Rate of CVD in patients with accelerated FEV1 decline compared to non-accelerated FEV1 decline using multiple CVD events (IRR 95% CI)