Declining Lung Function and Cardiovascular Risk: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—Pulmonary dysfunction predicts incident cardiovascular disease (CVD).

Objectives—To evaluate whether longitudinal decline in lung function is associated with incident heart failure (HF), coronary disease (CHD), and stroke.

Methods—Among 10,351 participants in the Atherosclerosis Risk in Communities Study free of CVD, rapid lung function decline was defined as the greatest quartile (n=2,585) of decline in either forced expiratory volume in 1 second (FEV_1; >1.9% decline/year) or forced vital capacity (FVC; >2.1% decline/year) over 2.9±0.2 years. The relationship between rapid decline in FEV_1 or FVC and subsequent incident HF, CHD, stroke, or a composite of these was assessed using multivariable Cox regression adjusting for the baseline spirometry value, demographics, height, body mass index, heart rate, diabetes, hypertension, LDL, use of lipid lowering medication, NT-proBNP and smoking.

Results—The mean age was 54 ± 6 years, 56% were women, and 81% were white. At 17±6 years of follow-up, HF occurred in 14%, CHD 11%, stroke 6%, and the composite 24%. Rapid decline in FEV_1 and in FVC were both associated with a heightened risk of incident HF (HR=1.17, 95% CI 1.04–1.33; p=0.010 and HR=1.27, 95% CI 1.12–1.44; p<0.001, respectively),

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with rapid decline in FEV_1 most prognostic in the first year of follow-up (HR=4.22, 95% CI 1.34–13.26; p=0.01). Rapid decline in FEV_1 was also associated with incident stroke (HR=1.25, 95% CI 1.04–1.50; p=0.015).

Conclusion—Rapid decline in lung function, assessed by serial spirometry, is associated with a higher incidence of subsequent CVD, particularly incident HF.

Keywords

lung function; FEV_1; FVC; cardiovascular disease; heart failure

Introduction

Cardiovascular disease is the leading cause of death in the United States, while chronic pulmonary disease is the third leading cause of mortality (1). Interactions between cardiac and pulmonary function in relation to clinical outcomes are well recognized (2). Impaired lung function is associated with nearly two-fold higher risk of cardiovascular mortality (3). Conversely, coronary heart disease (CHD) and heart failure (HF) are more common among people with pulmonary disease, even after accounting for common cardiovascular risk factors, including smoking.(4,5) Asthma and chronic obstructive pulmonary disease (COPD), the most prevalent respiratory diseases worldwide,(6) are associated with a systemic inflammatory response(7) and with systemic endothelial dysfunction and impaired vascular reactivity,(8) which also promote cardiovascular disease(9) and represent potential mechanisms underlying these cardiopulmonary interactions.

Age-related decline in lung function starts at approximately 25 years of age, with an average loss of 20 ml per year in the forced expiratory volume in one second (FEV_1).(10) Forced vital capacity (FVC) also declines with age to approximately 75% of the best value.(10) Environmental and behavioral factors, most notably cigarette smoking, in addition to genetics, interact to determine the speed of the decline in the lung function.(11) Rapid decline in lung function is a predictor of incident COPD.(12, 13) However, while rate of decline in lung function is associated with coronary disease mortality,(14,15) the association with incident cardiovascular events is not known. Furthermore, incipient or early heart failure may cause rapid deterioration in spirometric measures, and FEV1 in particular, due to interstitial and alveolar edema, and consequent airway compression.(16) However, rapid lung function decline secondary to early and undiagnosed HF (reserve causality) would be expected to predict incident HF during short-term – as opposed to long-term – follow-up. We hypothesize that greater decline in pulmonary function will be associated with a heightened risk of incident HF, stroke, coronary disease, and death over 20 year follow-up among middle-aged persons from a community-based sample free of prevalent cardiovascular disease.

Methods

Study population

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective cohort study of 15,792 persons, aged 45 and 64 years old at the time of recruitment.(17) Participants were

recruited using a probability sampling approach in four different centers in United States: Forsyth County, North Carolina; Jackson, Mississippi; the northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Since study inception (1987– 1989, Visit 1), four subsequent study visits were performed. Spirometry was performed at Visit 1 and at Visit 2 (1990–1992) in all participants attending each visit. The study was approved by institutional review boards from each site and all participants gave written informed consent.

For this analysis, we included participants who underwent spirometry as part of Visit 1(1987–1989) and Visit 2 (1990–1992). We excluded subjects with prevalent HF (n=700), CHD (n=661), and stroke (n=177) at Visit 2, those without information on HF (n=234) and death (n=1), and participants without spirometry data at Visits 1 or 2 (n=312; Supplemental Figure 1). We additionally excluded subjects with poor performance on spirometry as indicated by tests lasting less than 6 seconds or with irregular tracing; or with spirograms considered not reproducible (n=1912) following the previously published American Thoracic Society guidelines (18). A total of 10,351 participants were included in this analysis.

Assessment of lung function and rapid decline in lung function

Spirometry was performed following the American Thoracic Society guidelines at Visits 1 and 2.(18) Spirometry was conducted using a water-sealed Collins Survey II volume displacement spirometer (Collins Medical, Inc) and Pulmo-Screen II software (PDS Healthcare Products, 496 Inc). Three or more acceptable spirograms were obtained from at least 5 forced expirations. The best single spirogram was identified by a computer and confirmed by a technician (18). FEV_1 was assessed as the volume of gas exhaled in the first second of expiration. FVC was assessed as the volume of gas forcefully exhaled after maximal inspiratory effort. Equations for predicting FEV_1 and FVC were developed to obtain the percentage of predicted FEV_1 and FVC adjusted for age, sex, race, and height in ARIC Study.(19) The primary exposure variable for this analysis was the change in percent predicted FEV_1 between Visits 1 and 2 and the change in percent predicted FVC between Visits 1 and 2 (Visit 1 value –Visit 2 value for both). We primarily used FEV_1 and FVC as percentage of predicted instead of absolute values because the percentage predicted is a more reliable measurement of changes in spirometry over a time period of less than 5 years. (20) Supplemental analyses were performed with the FEV1/FVC ratio as the primary predictor.

Ascertainment of incident cardiovascular events

Incident HF, CHD, stroke and death were ascertained through 2012 from ongoing surveillance methods as previously described.(21,22) Incident HF was defined as the first occurrence of a hospitalization with a HF diagnosis according to the International Classification of Diseases-9th Revision (ICD-9) code 428 (428.0 to 428.9) in any position ascertained by ARIC Study retrospective surveillance of hospital discharges, or a death certificate with death from HF in any position or with an ICD-9 code of 428 or with an ICD-10 code of I50 among any of the listed diagnoses or underlying causes of death.(23) CHD was defined as a hospitalized acute myocardial infarction or CHD mortality. CHD was

ascertained from yearly follow-up phone calls, study visits, hospital discharge information on fatal and non-fatal myocardial infarction, next-of-kin interviews, physician-completed questionnaires, and death certification, and was adjudicated by the ARIC Mortality and Morbidity Classification Committee as previously described.(21) Stroke was defined as rapid onset of a focal neurological deficit lasting >24 hours or until death in the absence of a non-stroke cause. A stroke event was identified from annual phone calls, visits, or surveillance of ARIC community hospitals. A hospitalization was considered for validation of stroke event if the discharge diagnosis contained a cerebrovascular disease diagnosis code (ICD-9 codes 430 – 438), if the discharge summary included a key word related to cerebrovascular procedure or disease, or if there was imaging evidence of cerebrovascular disease. Following the National Survey of Stroke criteria for stroke definition,(24) a computerized algorithm and a physician reviewer independently classified strokes as definitive or probable.(22) Death was ascertained through linkage with the National Death Index.

Covariates

We used covariates measured at both Visit 1 and Visit 2. Race was self-reported. Hypertension was defined as systolic blood pressure   140 mmHg, diastolic blood pressure   90 mmHg, or use of antihypertensive medication. Body mass index (BMI) was calculated by dividing measured weight (in kilograms) by height (in meters) squared and was defined as previously described in ARIC.(25) Diabetes mellitus was defined as a baseline fasting glucose level   126 mg/dl, baseline non-fasting glucose level   200 mg/dl, self-reported physician diagnosis of diabetes or the presence of medication for diabetes. Smoking was assessed by an interviewer-administered questionnaire. Smoking history was ascertained by an interviewer-administered questionnaire, and categorized as never smokers, former smokers, and current smokers. Pack-years were obtained from the multiplication of average number of cigarette per day and number of years of smoking reported until visit 2 as previously described.(26,27) The N-terminal fragment of prohormone for BNP (NT-proBNP) and the high-sensitivity C reactive protein (hs-CRP) were measured from visit 2 serum samples that had previously been stored at $-70°C$. NT-proBNP measurements were performed with a sandwich immunoassay method on the Roche Elecsys 2010 Analyzer (Roche Diagnostics Corp, Indianapolis, IN). The assay coefficients of variation were 5.4% at an NT-proBNP value of 133 pg/mL and 4.3% at a value of 4516 pg/mL. High sensitivity CRP was measured using an immunoturbidimetric assay on the Roche Modular P chemistry analyzer (Roche Diagnostics, Indianapolis, IN). The coefficient of variation was 7.0%.(28)

Analytical approach

For each spirometry measure, initial quartile analysis suggested non-linear associations of change between Visits 1 and 2 and cardiovascular outcomes, with risk primarily associated with the greatest quartile of decline (Online Table 1). Therefore, change in each spirometric measure was dichotomized, with rapid decline defined as the greatest quartile of change between Visits 1 and 2. Non-rapid decliners were defined as those participants in the remaining three quartiles and served as the reference group. This approach is concordant with several prior publications assessing rapid decline in lung function.(14,29) Participant characteristics were described among rapid and non-rapid decliners. Categorical data were

reported as percent frequencies and compared by chi-squared test. Continuous normally distributed data were displayed as mean and standard deviation, and continuous non-normally distributed data were displayed as median and 25th percentile and 75th percentile. Comparisons of continuous variables between rapid decliners and non-rapid decliners were performed using t-test or Wilcoxon rank-sum test, accordingly.

Rates of incident HF, CHD, stroke, death, and the composite of these are presented as events per 1000 person-years at risk. The risk associated with rapid decline was assessed using multivariable Cox proportional hazards regression models with the non-rapid decliner group as the reference population. Three models were constructed adjusting for covariates selected based on prior literature. Model 1 was unadjusted; Model 2 adjusted for the baseline spirometry value, age, sex, race, and height; Model 3 additionally adjusted for ARIC field center, BMI, heart rate, low-density-lipoprotein cholesterol, use of lipid lowering medications, NT-proBNP, diabetes, hypertension, and smoking (smoking status and pack-years). Outcomes included HF, CHD, and stroke individually, the composite of these (HF, CHD, and stroke), and the composite of these events in addition to death (HF, CHD, and stroke, and death). Effect modification of age, race, and baseline spirometry on the relationship between rapid decline in lung function and cardiovascular outcomes was assessed using multiplicative interaction terms. The proportional hazards assumption was tested for all models. In analyses where a violation of the proportional hazards assumption was detected with the plots of log (−log (survival function)) vs. log (time) for the association between rapid decline in FEV_1 and HF, we also assessed the relationship over more restricted time intervals, partitioning the follow-up time as less than or more than one year, and as less than or more than ten years. These analyses were performed by placing landmarks at one and ten years respectively, and removing all patients that had a previous event or that had died. Second events were not taken into account. We assessed for competing risk of death for cardiovascular events using the Fine and Gray competing risks regression model to estimate the corresponding sub-distribution hazard ratio.(30) All statistical analyses were performed with STATA version 13.1 (Stata Corp., College Station, TX, USA). P-values <0.05 were considered statistically significant.

Results

Population characteristics

The mean age of the cohort was 53.7±5.7 years, 56% were women, and 81% were white (Table 1, Table 2). By definition, 25% of participants were classified as rapid decliners by the FEV_1 criteria of a >1.9%/year decrease in FEV_1, and 25% by the FVC criteria of a >2.1%/year decrease in FVC. 16% of participants met the definition of rapid decline by both FEV_1 and FVC criteria. Compared to ARIC participants included in this analysis, those not included due to poor quality or missing spirometry at Visit 2 tended to be older, more frequently black, with higher BMI and prevalence of hypertension, diabetes, and smoking (Online Table 2).

Rapid decline in FEV$_1$ and incident cardiovascular events

The mean annual rate of decline in percent predicted FEV$_1$ was 3.27 ± 1.79 %/year for FEV$_1$ rapid decliners and 0.02 ± 1.75 %/year for non-rapid decliners. Rapid decliners started with a higher FEV$_1$ in Visit 1 but ended with a lower FEV$_1$ at Visit 2 (Table 1). FEV$_1$ rapid decliners also demonstrated a greater annual decline in percent predicted FVC compared to non-rapid decliners (3.09 ± 2.63 %/year versus 0.37 ± 1.81 %/year, respectively).

Compared to non-rapid decliners, FEV$_1$ rapid decliners were older, more likely to be male, slightly taller, and had a higher prevalence of current smoking (Table 1). The prevalence of diabetes and hypertension were similar between groups, as were cholesterol levels. At Visit 1, BMI and blood pressure were not different among rapid and non-rapid decliners. However, by Visit 2, rapid decliners had higher BMI and blood pressure levels. High-sensitivity CRP, a marker of systemic inflammation, was significantly higher among rapid decliners (2.4 [1.2, 5.0] mg/L versus 2.0 [0.9, 4.1] mg/L, p <0.001). NT-proBNP assessed at Visit 2 was also higher among rapid decliners (53.8 [27.9, 99.7] pg/mL versus 47.8 [25.5, 84.7] pg/mL, p<0.001)

At a mean follow-up of 17 ± 6 years, cardiovascular disease occurred in 2490 (24%) participants. HF occurred in 1473 (14%), CHD in 1093 (11%), stroke in 664 (6%) and death in 2852 (28%) (Table 3). These incidence rates are similar to those reported in other general U.S. population studies.(31–34) FEV$_1$ rapid decliners showed a higher rate of incident cardiovascular disease compared to non-rapid decliners (composite of HF, CHD, and stroke; 16.7 (15.5–18.0)/1000 and 12.9 (12.3–13.5)/1000 person-years, respectively; Figure 1) After adjusting for baseline FEV$_1$, age, sex, race, height, ARIC center, body mass index, heart rate, low-density-lipoprotein cholesterol, NT-proBNP, diabetes, hypertension, and smoking, rapid FEV$_1$ decline remained associated with a higher risk of the composite endpoint (HR 1.15, 95% CI 1.04–1.26; p=0.004; Table 3 and Central Illustration). Rapid decliners also had a higher risk of death (Table 3). After accounting for competing risk of non-cardiovascular death, the risk of incident cardiovascular disease associated with rapid decline in FEV1 remained similar to that observed in the primary analysis (Table 3).

Rapid decliners had a higher risk of incident HF (HR 1.17, 95%CI 1.04–1.33; p=0.010), which persisted after excluding the 1093 subjects with incident CHD (HR 1.21, 95% CI 1.03–1.39; p=0.013). A violation of the proportional hazard assumption (p = 0.003) was observed for the relationship between decline in FEV$_1$ and incident HF, such that the risk associated with FEV1 rapid decline was greater during the early follow-up period and attenuated during late follow-up. For example, FEV$_1$ rapid decline was associated with a higher risk of HF in the first 1 year of follow-up (Table 4 and Figure 1; Supplemental Figure 2). Similarly, rapid decline was associated with a higher risk of HF during the first 10 years of follow-up but not after this point (Table 4). Rapid decline in FEV$_1$ was also associated with a heightened risk of stroke (HR 1.25, 95% CI 1.04–1.50; p=0.015; Table 3), with no evidence of a change in the magnitude of risk over the follow-up period. Rapid decline in FEV$_1$ was not associated with incident coronary disease (Table 3). In supplemental analyses using rapid decline in the FEV$_1$/FVC ratio, rapid decline in the ratio was similarly associated with incident HF, and the composite of HF, CHD, and stroke (Online Table 3).

Rapid decline in FVC and incident cardiovascular events

FVC rapid decliners had a lower FVC at Visit 1 compared to non-rapid decliners (Table 2), and demonstrated an annual decline of 3.70 ± 2.31 %/year compared to 0.17 ± 1.60 %/year for non-rapid decliners. FEV_1 was similar between these groups at baseline but demonstrated greater decline in the FVC rapid compared to non-rapid decline groups (2.69 ± 2.18 versus 0.17 ± 1.91%/year respectively; Table 2). FVC rapid decliners were older and more likely to be black. At Visit 1, they had higher BMI, heart rate, prevalence of hypertension, and active smoking (Table 2). These patterns persisted at Visit 2, but the magnitude of the difference in BMI, heart rate and blood pressure between groups was more prominent. Both hs-CRP and NT-proBNP were higher among rapid decliners (2.6 [1.2, 5.4] vs 1.9 [0.9, 4.0] mg/L, p <0.001; 53.4 [27.6, 98.9] vs 47.7 [25.7, 85.3] pg/mL, p<0.001 respectively).

FVC rapid decline was associated with a higher rate of the composite of incident HF, CHD, and stroke (incidence rate 16.6 (15.5–18.0)/1000 in rapid decliners and 12.6 (12.0–13.2)/1000 person-years in non-rapid decliners; Table 5, Figure 2). After full adjustment, rapid FVC decline was associated with a 20% higher risk of composite endpoint (HR 1.19, 95% CI 1.08–1.32, p<0.001; Table 5). FVC rapid decline was also associated with a heightened risk of death (Table 5). In competing risk models, death was not a significant competing risk for cardiovascular disease. For components of this composite, FVC rapid decline was associated with an increased risk of incident HF (HR 1.27, 95% CI 1.12–1.44; p<0.001), which persisted after excluding participants with incident CHD (HR 1.29, 95% CI 1.11–1.50; p=0.001). Unlike FEV_1 rapid decline, no significant variation in the risk associated with FVC rapid decline was noted through the follow-up period. No association was noted between FVC rapid decline and incident stroke or CHD (Table 4, Figure 2).

No heterogeneity of effect by race or sex was detected for the association between either rapid decline in FEV_1 or in FVC with heart failure, CHD, or stroke (all p for interaction >0.05). Baseline FEV_1 did significantly modify the relationship between rapid decline in FEV_1 and incident HF (p for interaction 0.004), such that the association of rapid decline in FEV_1 was only observed among participants with a percent predicted FEV_1<80% at baseline (Online Table 4). Baseline FEV_1 did not significantly modify the relationship between rapid decline in FEV_1 and the other outcomes assessed. Similarly, no interaction was noted between baseline FVC and the relationship between rapid decline in FVC and any of the studied outcomes. Similar associations with outcomes were noted when change in both percent predicted FEV_1 and percent predicted FVC were modeled as a continuous variables instead of categorical variables (Online Table 5). In a sensitivity analysis stratified by smoking status (current and former smokers versus never smokers), similar findings were noted as in the primary analysis (Online Tables 6 and 7). No heterogeneity of effect was noted, except for the relationship between rapid decline in FEV1 and incident CHD (p for interaction by smoking status =0.04) such that rapid decline in FEV1 predicted incident CHD among never smokers but not smokers. Similar findings as in the primary analysis were also noted after exclusion of participants with probable COPD at Visit 1 (2.5% of participants; Online Table 8).

Discussion

In a bi-racial community-based sample of 10,351 participants followed for approximately 17 years, rapid decline in lung function is associated with a higher risk of cardiovascular disease, independent of established cardiovascular risk factors (Central Illustration). Rapid decline in FEV_1 is associated with a higher incidence of HF, stroke and death, while rapid decline in FVC is associated with a higher incidence of HF and death. Notably, decline in FEV_1 was predictive of incident HF mainly in the first year of follow-up. In contrast, a consistent risk throughout the follow-up period was noted for the association of decline in FVC with incident HF, and for the association of both exposure measures with the other study endpoints. Neither sex nor race significantly modified these associations. These findings demonstrate that deterioration in lung function is a predictor of incident cardiovascular disease, independent of smoking status and baseline lung function.

Decline in lung function starts in young adulthood. An annual fall of 25–30 ml in FEV_1 is considered normal (13,35). Accelerated decline in pulmonary function results from a combination of genetic determinants and environmental exposure, and increases the risk of pulmonary diseases, mainly COPD.(36) Previous studies have shown an association between accelerated decline in lung function with systemic inflammatory activation (37), decline in arterial elasticity (38), and hypertension (39). Importantly, these same pathways have also been implicated in the development of atherosclerotic CHD,(40,41) ischemic stroke,(42) and HF.(43) Recent attention has focused on the role of co-morbidity driven systemic inflammation in the development of LV diastolic dysfunction and HFpEF in particular, (44,45) highlighting the potential parallel effects of inflammation on cardiac and pulmonary function. As a result of these shared pathophysiologic pathways, we therefore hypothesized that accelerated decline in pulmonary function would predict incident cardiovascular events. Indeed, participants with rapid decline in lung function in our analysis demonstrated higher concentrations of hsCRP – an established marker of systemic inflammation – compared to those without rapid decline. In the current study, FEV_1 rapid decline in lung function was defined as the greatest quartile of decline, with FEV_1 rapid decliners demonstrating an average decline of 120 ml/year, and FVC rapid decliners demonstrating an average 160 ml/ year decline. These values are consistent with prior studies of rapid decline in pulmonary function.(29) Both FEV_1 rapid decline and FVC rapid decline were predictive of incident cardiovascular disease independent of established cardiovascular risk factors and after accounting for the competing risk of non-cardiovascular death.

Rapid decline in both FEV_1 and FVC was associated with a higher risk of incident HF, even after adjusting for potentially confounding cardiovascular risk factors including smoking status and accounting for pack-years, and NT-proBNP. In addition, the association persisted after excluding participants with incident CHD, showing that incident CHD or myocardial infarction does not explain this association. We are not aware of other studies demonstrating a relationship between changes in lung function and HF risk. Prior studies have shown a relationship between low baseline lung function and incident HF (4,5,46) and have suggested that higher levels of inflammatory markers identify persons with poor lung function who are particularly high risk for HF (29). While the HF phenotype in these studies (HF with preserved [HFpEF] versus reduced [HFrEF] ejection fraction) is not clear,

impaired lung function appears differentially predictive of HFpEF compared to HFrEF(47) and the potential role for systemic inflammation in HFpEF has recently generated considerable interest.(44,45) Activation of inflammatory cascade may therefore be one mechanism linking lung function and HF, although further study is needed to support this hypothesis.(46) Previous studies showed an association between inflammation and impaired pulmonary function.(7) Indeed, the current analysis, hs-CRP - a marker of systemic inflammation - was significantly higher among FEV_1 and FVC rapid decliners than non-rapid decliners.

Rapid decline in FEV_1 was associated with heightened risk of subsequent HF hospitalization predominantly during the early follow-up period, with an attenuated magnitude of association later in the follow-up period, suggesting that reverse causality may be present such that FEV_1 decline in some cases may be an early manifestation of HF. In contrast, rapid decline in FVC was associated with HF risk consistently throughout follow-up. One explanation for these findings is that rapid decline in FEV_1 specifically may be largely an early manifestation of subclinical HF, with pulmonary congestion leading to interstitial and alveolar edema, consequent compression of the airways, and a rapid fall in FEV_1.(16) Indeed, rapid decline in FEV_1 secondary to early and undiagnosed HF (reserve causality) is expected to predict incident HF primarily during short-term follow-up, as observed in our analysis. In contrast, the consistent HF risk associated with rapid decline in FVC suggests a primary alteration in lung function predicting incident HF. Progressive deterioration in lung function may result in pulmonary hypertension and associated right heart failure when severe, although this is uncommon on a population level.(48) An alternative, or additional, explanation is shared pathophysiologic alterations including loss of elasticity in lung and vasculature,(38) and possibly the myocardium, with resulting coupled impairments in cardiovascular and pulmonary reserve. For any degree of cardiovascular dysfunction, impaired pulmonary function may then predispose to manifestation of HF signs and symptoms. Future studies with serial echocardiography and spirometry will be necessary to interrogate this hypothesis.

We noted differential independent associations of rapid decline in FEV1 with the atherosclerotic endpoints of stroke. The association between decline in FEV_1 and coronary disease mortality was previously demonstrated in the Copenhagen City Heart Study,(14) and Baltimore Longitudinal Study of Aging.(15) We also noted an association of rapid decline in FEV1 with incident CHD in unadjusted models and after adjustment for participant demographics. However, this association did not persist after further accounting for established cardiovascular risk factors. The reasons for these between study differences are unclear but may relate to differences in the populations studied and in the adjustment variables between studies. To the extent that inflammation is one mechanism mediating the relationship between decline in pulmonary function and incident cardiovascular disease, one potential explanation for this lack of association with CHD independent of established cardiovascular risk factors is that – for this endpoint at least – the additional contribution of pulmonary dysfunction to inflammation beyond established risk factors is modest. Similarly, in unadjusted analysis, both FEV_1 rapid decline and FVC rapid decline were associated with higher risk of stroke. However, only rapid decline in FEV_1 remained independently associated with incident stroke in fully adjusted models. Although reduced FEV has been

demonstrated as related to incident stroke,(49) to our knowledge, this is the first study demonstrating an association between rapid decline in FEV_1 and stroke. Inflammation-associated pro-atherosclerotic mechanisms may help explain this association. In addition, decline in lung function is associated with hypertension,(39) which is a major stroke risk factor and potential mediator.(42) In our analysis, the association of rapid decline in FEV_1 and incident stroke persisted after accounting for hypertension and blood pressure. Low pulmonary function has been associated with a higher risk of atrial fibrillation.(50) Although the relationship between changes in lung function and incident atrial fibrillation is not known, a higher incidence of atrial fibrillation among the rapid decline group is also a possible explanation. Finally, rapid decline in lung function is associated with a higher incidence of COPD,(13,36) which may in turn lead to higher levels of haematocrit and hemoglobin, and could predispose to stroke through elevation in the blood viscosity.(51) However, we did not find any indication that hemoglobin is a mediator in the relationship between decline in FEV_1 and stroke in our analysis (data not shown).

Current guidelines recommend serial spirometry for individuals at higher risk of developing pulmonary disease, such as heavy smokers and workers with an occupational exposure.(20) Our results provide additional evidence that, in addition to providing information regarding risk of pulmonary disease, serial changes in spirometry also provides the clinician information regarding the risk of cardiovascular disease. Our findings also demonstrate that rapid decline in FEV_1 in particular predicts increase risk of incident HF. This risk was particularly high, 4-fold increased, within 12 months, suggesting that clinicians should carefully consider incipient HF in patients with rapid changes in FEV_1. Further studies are necessary to determine whether strategies to reduce the rate of decline in FEV_1 and FVC reduce the incidence of cardiovascular diseases.

Some limitations in our analyses should be noted. The 3-year period between the two spirometry tests is relatively short and test-retest variability may limit our ability to identify participants with actual accelerated decline in lung function impairment. However, spirometry is a reliable and reproducible test, with a coefficient of variation within subjects of about 5%,(52) making variability between the two tests unlikely to bias our findings. Only pre-bronchodilator spirometric measurements are available in this study, although post-bronchodilator measures are also recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).(11) Finally, unmeasured and residual confounding of the relationship between change in lung function and cardiovascular outcomes could not be completely addressed by multivariate modeling.

Conclusions

Rapid decline in lung function over a 3-year period is associated with a heightened risk of incident cardiovascular disease, including HF and stroke, independent of established cardiovascular risk factors and smoking. Rapid decline in FVC is associated with heighten risk of HF throughout the approximately 17 year follow-up period, while rapid decline in FEV_1 specifically predicts a 4-fold increase in the risk of incident HF at 1 year, and could be an early manifestation of HF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABREVIATIONS LIST

CHD	coronary disease
CVD	cardiovascular disease
COPD	chronic obstructive pulmonary disease
BMI	body mass index
FEV$_1$	forced expiratory volume in 1 second
FVC	forced vital capacity
HF	heart failure

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CLINICAL PERSPECTIVES

Competencies in Patient Care

In addition to predicting pulmonary disease, a rapid decline in spirometric measures of lung function, FEV_1 and FVC is associated a higher risk of cardiovascular disease. Specifically, rapid decline in FEV_1 is associated with a 4-fold increased risk of incident heart failure during the first 12 months of follow-up, suggesting that clinicians should be alert to manifestation of heart failure when patients exhibit rapid deterioration of FEV_1.

Translational Outlook

Further studies are necessary to determine whether worsening of these indices of pulmonary function reflect incipient heart failure and whether strategies to retard the decline in lung function can prevent or delay the onset of cardiovascular disease.
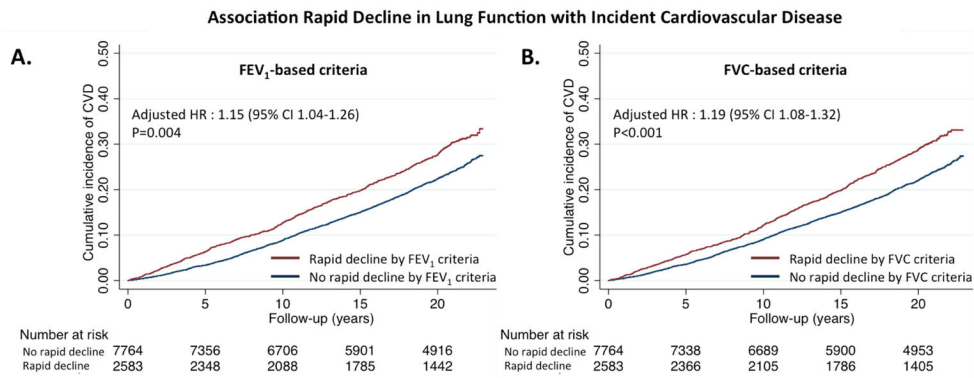
Figure 1. Association of rapid decline in FEV_1 with incident cardiovascular disease

Rapid decline is defined as greatest quartile of decline in FEV_1 over a mean of 2.9 years. Kaplan-Meier curves demonstrate the rates of (A) incident heart failure, (B) incident coronary heart disease, (C) incident stroke, and (D) the composite of these among the rapid decliner and non-rapid decliner groups. Hazard ratios (HR) and associated 95% confidence intervals are calculated from Cox regression models adjusted for age, sex, race, ARIC center, height, heart rate, body mass index, LDL-cholesterol, NT-proBNP, diabetes, hypertension, and smoking. For heart failure, a violation of the proportional hazards assumption was noted for this endpoint, indicated by the significant p for interaction for decline in percentage of predicted FEV_1 and time with respect to incident heart failure. The Panel A inset shows the Kaplan-Meier curve restricted to the 1st year of follow-up. HRs are provided separately for pre-1 year and post-1year follow-up (indicated by dashed line), with associated P for interaction.
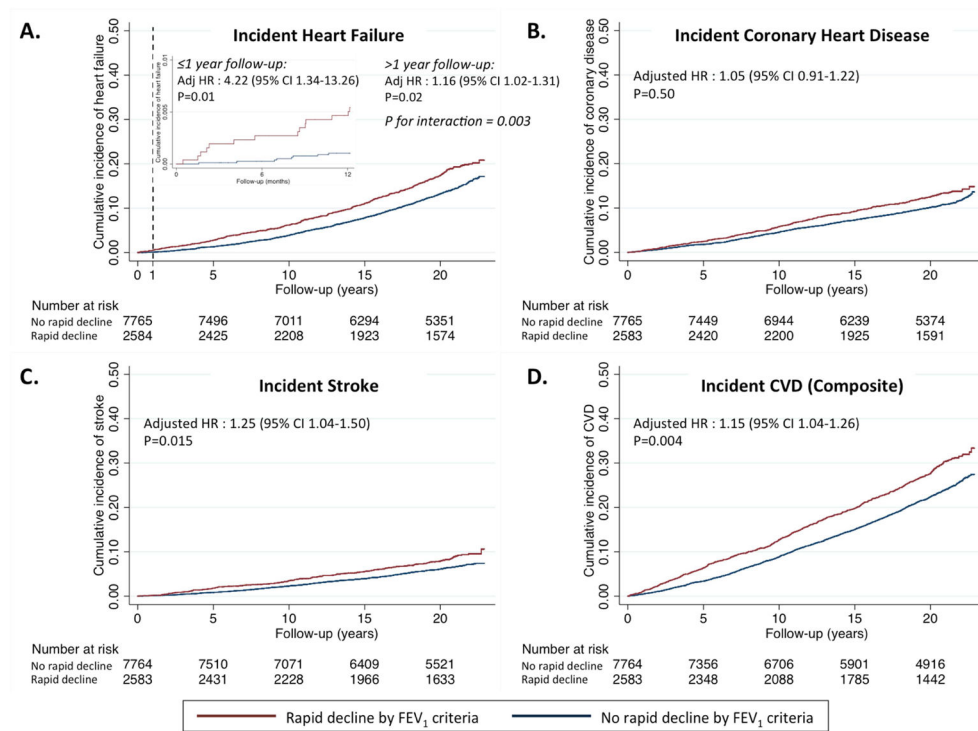
Figure 2. Association of rapid decline in FVC with incident cardiovascular disease
Rapid decline is defined as greatest quartile of decline in FVC over a mean of 2.9 years.
Kaplan-Meier curves demonstrate the rates of (A) incident heart failure, (B) incident
coronary heart disease, (C) incident stroke, and (D) the composite of these among the rapid
decliner and non-rapid decliner groups. Hazard ratios (HR) and associated 95% confidence
intervals are calculated from Cox regression models adjusted for age, sex, race, ARIC
center, height, heart rate, body mass index, LDL-cholesterol, NT-proBNP, diabetes,
hypertension, and smoking.
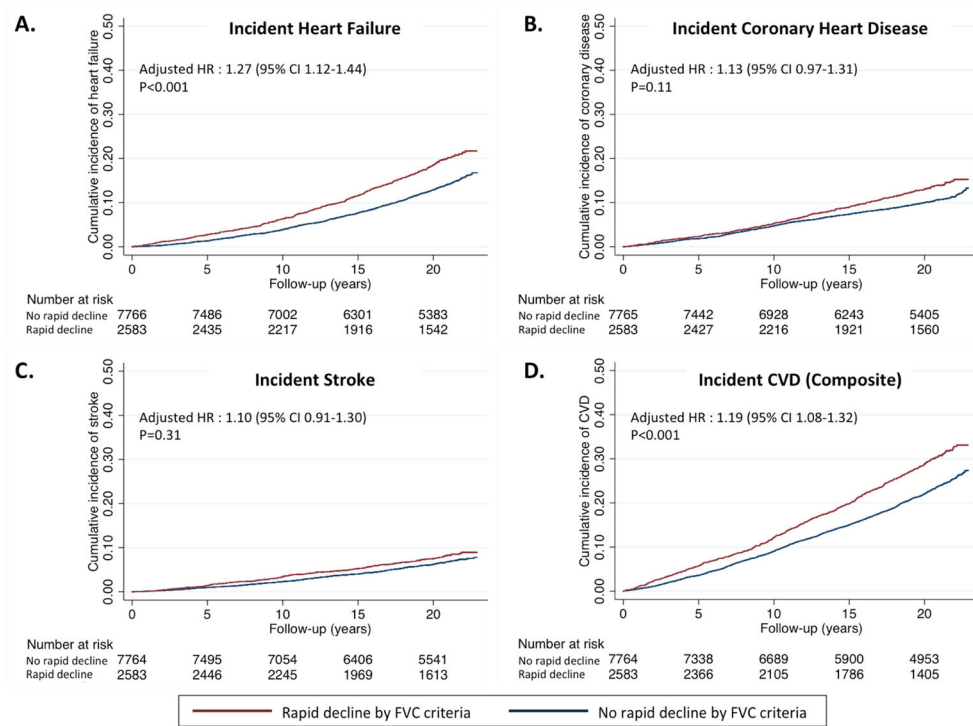
Central Illustration. Association of Rapid Decline in Lung Function With Subsequent Cardiovascular Disease

Rapid decline is defined as the greatest quartile of decline in either FEV_1 (Panel A) or FVC (Panel B) over a 2.9 year period. Kaplan-Meier curves demonstrate rates of subsequent cardiovascular disease (CVD) among the rapid decliner and non-rapid decliner groups. CVD is defined as a composite of heart failure, coronary disease, and stroke. Hazard ratios (HR) and associated 95% confidence intervals are calculated from Cox regression models adjusted for age, sex, race, ARIC center, height, heart rate, body mass index, LDL-cholesterol, NT-proBNP, diabetes, hypertension, and smoking.

Table 1

Baseline characteristics according to the decline in percentage of predicted FEV$_1$

Characteristics	Visit 1			Visit 2		
	Rapid decliners n= 2,585	Non-rapid decliners n= 7,766	p	Rapid decliners n= 2,585	Non-rapid decliners n= 7,766	p
Demographics						
Age –years	54.4 ± 5.7	53.5 ± 5.6	<0.001	57.7 ± 5.7	56.9 ± 5.6	<0.001
Male gender (%)	1236 (48)	3307 (43)	<0.001	-	-	-
Race – White (%)	2097 (81)	6234 (80)	0.31	-	-	-
Center			<0.001			-
Forsyth (%)	727 (28)	1990 (26)		-	-	-
Jackson (%)	418 (16)	1337 (17)		-	-	-
Minneapolis (%)	881 (34)	2286 (29)		-	-	-
Washington (%)	559 (22)	2153 (28)		-	-	-
Medical History						
Hypertension (%)	744 (29)	2176 (28)	0.45	881 (34)	2290 (30)	<0.001
Anti-hypertensive medications (%)	618 (24)	1793 (23)	0.38	591 (23)	1705 (22)	0.30
Diabetes (%)	211 (8)	634 (8)	0.99	319 (12)	906 (12)	0.34
LDL cholesterol	137 ± 38	137 ± 38	0.86	134 ± 37	133 ± 36	0.20
Lipid lowering medications (%)	68 (3)	187 (2)	0.53	122 (5)	441 (6)	0.06
Smoking Status			<0.001			<0.001
Current (%)	762 (30)	1656 (21)		731 (28)	1500 (19)	
Former (%)	851 (33)	2578 (33)		961 (37)	2981 (38)	
Never (%)	964 (37)	3530 (46)		892 (35)	3283 (42)	
NT-proBNP (pg/mL)	-	-	-	54 [28 – 100]	48 [26 – 85]	<0.001
hs-CRP (mg/L)	-	-	-	2.4 [1.2 – 5.0]	2.0 [0.9 – 4.1]	<0.001
Physical Exam						
Height - cm	168.9 ± 9.2	168.3 ± 9.3	0.001	-	-	-
BMI(kg/m^2)	27.3 ± 5.0	27.2 ± 4.9	0.48	28.3 ± 5.4	27.4 ± 5.0	<0.001
Heart rate - bpm	66.2 ± 9.9	66.1 ± 9.7	0.59	65.7 ± 10.3	65.3 ± 9.6	0.073
Systolic BP (mmHg)	119.8 ± 17.3	119.3 ± 17.2	0.21	123.1 ± 18.6	119.5 ± 17.4	<0.001
Diastolic BP (mmHg)	72.9 ± 10.8	73.0 ± 10.5	0.57	72.8 ± 10.4	71.7 ± 9.8	<0.001

Characteristics	Visit 1			Visit 2		
	Rapid decliners n= 2,585	Non-rapid decliners n= 7,766	p	Rapid decliners n= 2,585	Non-rapid decliners n= 7,766	p
Spirometry						
FEV$_1$ (liters)	2.96 ± 0.77	2.91 ± 0.74	0.009	2.60 ± 0.74	2.84 ± 0.72	<0.001
FEV$_1$ (liters/yr)	-	-	-	0.12 ± 0.06	0.02 ± 0.05	<0.001
% predicted FEV$_1$ (%/yr)	-	-	-	3.27 ± 1.79	0.02 ± 1.75	-
FVC (liters)	4.00 ± 0.99	3.89 ± 0.97	<0.001	3.60 ± 0.97	3.78 ± 0.94	<0.001
FVC (liters/yr)	-	-	-	0.14 ± 0.11	0.04 ± 0.07	<0.001
% predicted FVC (%/yr)	-	-	-	3.09 ± 2.63	0.37 ± 1.81	<0.001

FEV1: forced expiratory volume in 1 second; BMI: body mass index; FVC: forced vital capacity; : delta; % predicted FEV1 per year: delta in the percentage of predicted FEV1; % predicted FVC: delta in the percentage of predicted FVC per year. BP: blood pressure; LDL: low-density cholesterol.

Table 2

Baseline characteristics according to the decline in percentage of predicted FVC

Characteristics	Visit 1			Visit 2		
	Rapid decliners n=2,585	Non-rapid decliners 7,766	p	Rapid decliners n=2,585	Non-rapid decliners 7,766	p
Demographics						
Age –years	54.6 ± 5.7	53.4 ± 5.6	<0.001	58.0 ± 5.7	56.8 ± 5.6	<0.001
Male gender (%)	1113 (43)	3430 (44)	0.32	-	-	-
Race – White (%)	2029 (79)	6302 (81)	0.003	-	-	-
Center	-	-	<0.001	-	-	-
Forsyth (%)	898 (35)	1819 (23)		-	-	
Jackson (%)	467 (18)	1288 (17)		-	-	
Minneapolis (%)	667 (26)	2500 (32)		-	-	
Washington (%)	553 (21)	2159 (28)		-	-	
Medical History						
Hypertension (%)	805 (31)	2115 (27)	<0.001	904 (35)	2267 (29)	<0.001
Anti-hypertensive medications (%)	673 (26)	1738 (22)	<0.001	639 (25)	1657 (21)	<0.001
Diabetes (%)	214 (8)	631 (8)	0.81	334 (13)	891 (12)	0.046
LDL cholesterol	136.7 ± 37.4	137.0 ± 38.8	0.7385	134.2 ± 36.8	132.7 ± 36.1	0.077
Lipid lowering medications (%)	78 (3)	177 (2)	0.036	118 (5)	445 (6)	0.024
Smoking status	-	-	<0.001	-	-	<0.001
Current (%)	730 (28)	1688 (22)		693 (27)	1538 (20)	
Former (%)	848 (33)	2581 (33)		954 (37)	2988 (39)	
Never (%)	1000 (39)	3494 (45)		937 (36)	3238 (42)	
NT-proBNP (pg/mL)	-	-	-	54 [28 – 99]	48 [26 – 85]	<0.001
hs-CRP (mg/L)	-	-	-	2.6 [1.2 – 5.4]	1.9 [0.9 – 4.0]	<0.001
Physical Exam						
Height - cm	168.3 ± 9.4	168.6 ± 9.3	0.17	-	-	-
BMI(kg/m^2)	27.5 ± 5.0	27.2 ± 5.0	0.002	28.6 ± 5.4	27.3 ± 5.0	<0.001
Heart rate - bpm	66.5 ± 9.8	66.1 ± 9.8	0.047	66.0 ± 10.2	65.2 ± 9.6	<0.001
Systolic BP (mmHg)	120.1 ± 17.6	119.2 ± 17.1	0.024	123.2 ± 18.5	119.5 ± 17.5	<0.001
Diastolic BP (mmHg)	72.8 ± 10.7	73.1 ± 10.5	0.15	72.7 ± 10.4	71.7 ± 9.8	<0.001

Characteristics	Visit 1				Visit 2			
	Rapid decliners n=2,585	Non-rapid decliners 7,766	p		Rapid decliners n=2,585	Non-rapid decliners 7,766	p	
Spirometry								
FEV_1 (liters)	3.95 ± 0.99	3.95 ± 0.99	0.065		2.56 ± 0.73	2.85 ± 0.72	<0.001	
FEV_1 (liters/yr)	-	-	-		0.10 ± 0.07	0.03 ± 0.05	<0.001	
% predicted FEV_1 (%/yr)	-	-	-		2.69 ± 2.18	0.17 ± 1.91	<0.001	
FVC (liters)	2.86 ± 0.76	2.94 ± 0.74	<0.001		3.49 ± 0.94	3.82 ± 0.94	<0.001	
FVC (liters/yr)	-	-	-		0.16 ± 0.10	0.03 ± 0.06	<0.001	
% predicted FVC (%/yr)	-	-	-		3.70 ± 2.31	0.17 ± 1.60	-	

FVC: forced vital capacity; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; : delta; % predicted FEV_1 per year: delta in the percentage of predicted FEV_1; % predicted FVC: delta in the percentage of predicted FVC per year; BP: blood pressure; LDL: low–density cholesterol.

Table 3

Risk of cardiovascular disease according to decline in percentage of predicted FEV$_1$

Outcomes	n	Events	Incidence rate/1000p-y	Model 1 HR (95%CI)	p	Model 2 HR (95%CI)	p	Model 3 HR (95%CI)	p
Heart failure									
Non-rapid decliners	7766	1043	7.2 (6.8–7.7)	Ref		Ref		Ref	
Rapid decliners	2585	430	9.5 (8.6–10.4)	1.35 (1.20–1.51)	<0.001	1.31(1.17–1.46)	<0.001	1.17(1.04–1.33)	0.010
Coronary disease									
Non-rapid decliners	7766	786	5.5 (5.1–5.9)	Ref		Ref		Ref	
Rapid decliners	2585	307	6.6 (5.9–7.4)	1.24 (1.08–1.41)	0.002	1.16(1.02–1.33)	0.028	1.05(0.91–1.22)	0.50
Stroke									
Non-rapid decliners	7766	467	3.1 (2.9–3.5)	Ref		Ref		Ref	
Rapid decliners	2585	196	4.3 (3.7–4.9)	1.35 (1.15–1.60)	<0.001	1.29(1.09–1.52)	0.003	1.25(1.04–1.50)	0.015
Death									
Non-rapid decliners	7766	1989	13.1 (12.5–13.7)	Ref		Ref		Ref	
Rapid decliners	2585	863	17.9 (16.8–19.2)	1.41 (1.30–1.52)	<0.001	1.32 (1.22–1.43)	<0.001	1.18 (1.08–1.28)	<0.001
Composite endpoint without death									
Non-rapid decliners	7766	1759	12.9 (12.3–13.5)	Ref		Ref		Ref	
Rapid decliners	2585	706	16.7 (15.5–18.0)	1.31 (1.20–1.43)	<0.001	1.25 (1.15–1.36)	<0.001	1.15 (1.04–1.26)	0.004
Composite endpoint including death									
Non-rapid decliners	7766	2849	20.5 (19.9–21.3)	Ref		Ref		Ref	
Rapid decliners	2585	1160	26.9 (25.4–28.5)	1.34 (1.25–1.43)	<0.001	1.26 (1.18–1.35)	<0.001	1.14 (1.06–1.23)	<0.001

Model 1: unadjusted; Model 2: adjusted for baseline FEV1, age, sex, race, and height; Model 3: additionally adjusted for ARIC center, body mass index, heart rate, low-density-lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking. Composite endpoint includes heart failure, stroke, and coronary disease. FEV1: forced expiratory volume in 1 s; HR (95%CI): hazard ratio and 95% confidence interval.

Table 4

Risk of heart failure associated with rapid decline in lung function defined based on percentage of predicted FEV_1 stratified by follow-up time (≤ or > 1 year or 10 years)

1 year			>1 year			10 year			>10 year		
Events	HR (95%CI)	p	Events	HR (95%CI)	p	Events	HR (95%CI)	p	Events	HR (95%CI)	p
22	4.22 (1.34–13.26)	0.014	1451	1.16 (1.02–1.31)	0.023	445	1.47 (1.18–1.83)	0.001	1028	1.07 (0.92–1.24)	0.40

FEV_1: forced expiratory volume in 1 s; HR (95%CI): hazard ratio and 95% confidence interval. HRs are from a fully adjusted Model 3: baseline FEV_1, age, sex, race, height, ARIC center, body mass index, heart rate, low-density-lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking.

Table 5

Risk of cardiovascular disease according to decline in percentage of predicted FVC

Outcomes	n	Events	Incidence rate/1000p-y	Model 1 HR (95%CI)	p	Model 2 HR (95%CI)	p	Model 3 HR (95%CI)	p
Heart failure									
Non-rapid decliners	7766	1021	7.1 (6.6–7.5)	Ref		Ref		Ref	
Rapid decliners	2585	452	10.0 (9.1–11.0)	1.46 (1.31–1.64)	<0.001	1.49 (1.33–1.67)	<0.001	1.27 (1.12–1.44)	<0.001
Coronary disease									
Non-rapid decliners	7766	779	5.4 (5.0–5.8)	Ref		Ref		Ref	
Rapid decliners	2585	314	7.3 (6.6–8.2)	1.31 (1.15–1.49)	<0.001	1.31 (1.14–1.49)	<0.001	1.13 (0.97–1.31)	0.11
Stroke									
Non-rapid decliners	7766	481	3.3 (3.0–3.6)	Ref		Ref		Ref	
Rapid decliners	2585	182	4.0 (3.4–4.6)	1.23 (1.03–1.46)	0.019	1.18 (0.99–1.41)	0.061	1.10 (0.91–1.30)	0.31
Death									
Non-rapid decliners	7766	1975	12.9 (12.4–13.6)	Ref		Ref		Ref	
Rapid decliners	2585	877	18.3 (17.1–19.6)	1.46 (1.35–1.58)	<0.001	1.43 (1.32–1.55)	<0.001	1.27 (1.16–1.39)	<0.001
Composite endpoint without death									
Non-rapid decliners	7766	1748	12.6 (12.0–13.2)	Ref		Ref		Ref	
Rapid decliners	2585	717	16.6 (15.5–18.0)	1.35 (1.24–1.47)	<0.001	1.36 (1.25–1.49)	<0.001	1.19 (1.08–1.32)	<0.001
Composite endpoint including death									
Non-rapid decliners	7766	2835	20.4 (19.7–21.2)	Ref		Ref		Ref	
Rapid decliners	2585	1174	27.3 (25.8–28.9)	1.37 (1.28–1.47)	<0.001	1.36 (1.27–1.46)	<0.001	1.21 (1.12–1.30)	<0.001

Model 1: unadjusted; Model 2: adjusted age, sex, race, and height; Model 3: additionally adjusted for ARIC center, body mass index, heart rate, low-density-lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking. Composite endpoint includes heart failure, stroke, and coronary disease.

FVC: forced vital capacity; HR (95%CI): hazard ratio and 95% confidence interval.