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Lung function and cardiovascular disease: a link

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Abstract

The relationship between lung and heart diseases has long been recognized, with necropsy studies demonstrating silent myocardial infarctions or coronary artery calcification in patients with advanced emphysema as the death cause. Improvements in non-invasive techniques and epidemiologic approaches established that lung and cardiovascular diseases frequently coexist in mid and late life. Even among those without diagnosed lung disease, lower than expected forced vital capacity, forced expiratory volume in 1 second, and their ratio each portend greater risk of developing cardiovascular risk factors including hypertension, obesity, and metabolic syndrome, and for incident cardiovascular diseases including left heart failure, atrial fibrillation and stroke. Greater longitudinal declines in these spirometric measures are further associated with cardiovascular morbidity and mortality. While obstructive ventilatory patterns are more common, restrictive ventilatory patterns seem to demonstrate an independent and more robust association with cardiovascular diseases such as heart failure. These subclinical alterations in pulmonary function also relate to subclinical abnormalities of cardiac structure and function. Although the biologic pathways linking pulmonary and cardiovascular dysfunction are not clear, chronic systemic inflammation appears to be one important underlying pathophysiologic link. Despite the growing evidence of lung dysfunction as a cardiovascular risk factor, spirometric evaluation is still underutilized in clinical practice, particularly among cardiac patients, and optimal therapeutic and preventive strategies are still unclear. In this review, we address the current knowledge and controversies regarding the links between lung function and cardiovascular disease.

Keywords

COPD; restrictive lung disease; heart failure; cardiovascular disease; risk factors

Introduction

Lung function encompasses airway flow, volumes and capacities, and oxygenation. The anatomic and physiologic continuity of the lungs with the heart and vessels intuitively

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suggests that impairments in any component of lung function may impact cardiovascular health. Early necropsy studies highlighted the co-existence of pulmonary diseases – both obstructive and restrictive – with cardiovascular disease (CVD) (1). While the mechanisms potentially linking pathology of these two organ systems were unclear, shared risk factors were well recognized, including smoking. Beyond coronary disease, the associations of pulmonary diseases with impairments in cardiac function were also well-recognized, most prominently *cor pulmonale*(1).

Pulmonary disease of lesser severity or subclinical pulmonary dysfunction may also impact cardiovascular function and cardiovascular disease. Spirometry is one of the simplest and most widely available methods to assess pulmonary function. Abnormalities of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and FEV1/FVC ratio are each associated with higher prevalence of cardiovascular risk factors and risk of cardiovascular diseases. Furthermore, the extent of subclinical lung dysfunction, age of onset, and rate of decline have also been consistently associated with heightened risk of cardiovascular disease. The association of pulmonary disease with right heart failure has been recently reviewed extensively by others (2, 3). In this review we will focus on the primary relationships of pulmonary disease and dysfunction with common incident cardiovascular disease and with alterations in cardiac structure and function.

Prevalent pulmonary diseases and cardiovascular disease

The prevalence of cardiovascular diseases among persons with COPD varies considerably across studies related to differences in sample selection and diagnostic criteria, with estimates ranging from 2 to 70%(4). Despite this variability, several large epidemiological studies demonstrate an association between COPD and higher prevalence of CV risk factors and prevalent CV disease, which is stronger at older ages. In addition to a higher prevalence of ever smoking, participants in these studies with COPD tend to demonstrate higher prevalence of hypertension and diabetes after accounting for demographic characteristics.(4) Several studies also demonstrate higher prevalence of manifest cardiovascular disease. In one meta-analysis of several epidemiologic cohort studies(4), persons with COPD had higher odds of being diagnosed with any cardiovascular disease (TABLE). Among patients with COPD, CVD is a common cause of hospitalization (approximately 42% for 1st admission and 48% for readmission in the Lung Health Study)(5), with HF as the leading cause of hospitalization(6).

A restrictive pulmonary pattern, typically defined as a reduction in lung volumes and total lung capacity without signs of airway obstruction, is also associated with an increased prevalence of CVD. While obstructive pulmonary disorders primarily include COPD and asthma, restrictive ventilatory patterns may be due to a wide list of etiologies, intrinsic and extrinsic to respiratory system. These include alterations in the lung parenchyma, pleura, chest wall or neuromuscular apparatus(7). Using only spirometric variables, a restrictive ventilatory pattern can be defined as a reduction in the forced vital capacity (FVC) without airway obstruction (normal FEV1/FVC). Prevalence estimates for restrictive ventilatory pattern range from 3 to 12% in the overall population(8, 9). The presence of a restrictive ventilatory pattern is independently associated with obesity and metabolic syndrome(10),

dyslipidemia(11) and hypertension (12). Compared to those with normal spirometry, individuals with a restrictive ventilatory pattern demonstrated a higher prevalence of CVD independent of common CV risk factors (adjusted OR 2.3; 95% CI 1.9-2.9). Notably, this magnitude of association was larger than that observed for an obstructive pattern in this study(9). Using pletismographic total lung capacity, the gold standard technique to diagnose a “restrictive pattern”, similar associations with heightened CVD risk were observed as when using FVC criteria alone. The presence of a restrictive ventilatory pattern has also been shown to be predictive of all-cause and cardiovascular mortality(13, 14), with death predominantly from cardiac origin (39%), while respiratory and lung cancer caused less than 10% of fatal events(13).

Subclinical pulmonary dysfunction and cardiovascular disease

Data from several longitudinal cohort studies have demonstrated an association between impairments in lung function – even in the absence of clinical pulmonary disease – and heightened cardiovascular risk. In an analysis of 3 cohorts [Framingham Offspring Study (FOC), Coronary Artery Risk Development in Young Adults Study (CARDIA), and Framingham Generation III cohort (GenIII)], an FEV1 <80% predicted in early adulthood (25-49 years) was associated with a higher prevalence of both respiratory and cardiovascular diseases in later life (>20 years of follow up) in each cohort. Notably, participants with an impaired FEV1 at baseline also received their first comorbid diagnosis on average a decade earlier compared to those with FEV1 >80% predicted (15). Similarly, among 1,861 participants in NHANES 1 aged 40-60 years, the worst quintile of FEV1 (mean percent predicted FEV1 of 63%) was associated with a >2-fold increase in incident cardiovascular death or hospitalization (RR 2.44; 1.37–4.33) compared to the best quintile of FEV1 (mean percent predicted FEV1 109%)(16). Furthermore, even those in the third quintile with a mean percent predicted FEV1 of 88%, generally considered normal, demonstrated a heightened risk of CV events compared to the best quintile (RR 1.78; 1.18–2.70) after adjusting for Framingham risk score, age, smoking, gender, diabetes, systolic and diastolic BP, cholesterol, BMI, race, and treated hypertension (16). Similar findings were observed among a younger sample from the CARDIA study (n=4,761, mean age 24.9±3.6 years)(17). In this study, lower percent predicted FEV1 and FVC, but not FEV1/FVC ratio, was associated with greater risk of the composite of fatal and non-fatal cardiovascular events independent of age, gender, race, education, baseline body mass index, smoking, diabetes, systolic blood pressure, use of anti-hypertensive medication, total and HDL-cholesterol. Worse FVC in particular was also independently associated with greater risk for incident left heart failure (LHF) (17).

Beyond lung function at a single timepoint, deterioration in lung function – even over relatively short time periods – also predicts worse cardiovascular outcomes, and LHF in particular. In the ARIC cohort, rapid decline in lung function over approximately 3 years, defined as the worst quartile of change in FEV1 (reduction in >1.9% per year) or FVC (decline in >2.1% per year), was independently associated with a heightened risk of incident LHF (TABLE)(18). Interestingly, the relationship of LHF with the decline in FEV1 (but not FVC) was strongest during the first year of follow-up (HR 4.22; 1.34–13.26), with significant but more modest associations noted up to 10-year follow-up (1.47; 1.18–1.83).

This may be due to reverse causality with rapid FEV1 decline representing an early manifestation of LHF secondary to pulmonary congestion and alveolar edema, or alternatively rapid deterioration of pulmonary function secondary to parenchymal disease may accelerate HF development or symptom manifestation.

The association of lung function decline with future cardiovascular disease, and incident LHF in particular, persisted after accounting for several confounders in several cohorts(17, 19). Interestingly, low FEV1 or FEV1 decline was strongly associated with incident LHF in cohorts where participants were middle aged and older (average >45 years at baseline) independently of traditional and non-traditional risk factors(18–21). In contrast, in the younger CARDIA cohort (average 26 years at baseline), FVC decline was more robustly associated with incident LHF, while FEV1 and FEV1/FVC ratio were not(17). The reasons for these differences in the associations of lung function measures with LHF between cohorts and age groups are unclear. Regardless, these findings suggest that the impact of distinct lung function patterns – and their decline – on CV outcomes, and LHF in particular, appears to differ by age.

Worsened FEV1 also relates to subclinical atherosclerosis and incident coronary artery disease(22), although these associations are attenuated after accounting for traditional risk factors (18, 23). While incident stroke risk was associated with rapid decline of FEV1 (adjusted OR 1.30; 1.06-1.59) and FVC (adjusted OR 1.32; 1.06-1.65) in the CARDIA cohort(17), in ARIC cohort only FEV1 remained associated with stroke when accounting for age, sex, race, height, body mass index, heart rate, low-density lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking (HR 1.25, 1.04–1.50; p=0.015) (18). Impaired lung function is also an independent risk factor for atrial fibrillation (AF) (24–26). Both lower FEV1 and FVC are associated with greater incidence of AF independent of HF or other cardiovascular diseases(24). Interestingly, in a report from 15,004 participants in the ARIC cohort study, the association of lower FEV1 and FEV1/FVC ratio with incident AF was appreciably attenuated after adjusting for inflammatory biomarkers, suggesting that some of this risk may be mediated by inflammation. (26) Other potential mechanisms that have been proposed include associated left ventricular hypertrophy and diastolic dysfunction, alterations in structure and function of pulmonary veins originating ectopic beats, and increased sympathetic drive.(24–26).

Subclinical pulmonary dysfunction is also associated with incident hypertension, a major risk factor for cardiovascular morbidity and mortality. Among 3205 young adults in CARDIA, decline in FVC (highest FVC at year 0, 2 or 5 of the study minus FVC at year 10) was associated with the development of incident hypertension between ages 35 to 45 years old (12). Participants whose decline in FVC was greater than 250 mL, even if the FVC remained in the normal range, had a significantly higher risk of developing hypertension compared to those without decline in adjusted models. Small artery elasticity has been directly associated with FVC, and one proposed explanation for the association of changes in FVC with incident hypertension is therefore a common pathophysiologic process of arterial stiffness and loss of elastic recoil of the lung tissue(27). Rapid lung function decline has also been linked to heightened risk of developing metabolic syndrome, independent of BMI. While the mechanical impact of abdominal obesity on ventilatory impairment may

certainly contribute, metabolically active regional fat depots may also contribute through increasing levels of pro-inflammatory adiponectins stimulated by chronic or intermittent hypoxia, which can be an additional source for systemic inflammation(11).

Pulmonary dysfunction and subclinical cardiovascular disease and dysfunction

In addition to associations with incident cardiovascular disease, subclinical impairments in lung function are also associated with subclinical impairments in cardiac structure and function. Investigators from the MESA cohort studied the relationship of milder chronic lung disease with ventricular structure and function in 2816 participants aged 45-84 years who underwent spirometry, chest computed tomography, and cardiac magnetic resonance imaging. They found a linear inverse relationship between greater percent emphysema – across the spectrum from normal to severe disease without a threshold effect - and lower left ventricle end-diastolic volume and stroke volume. These associations were more robust in smokers. Furthermore, greater magnitude of airflow obstruction was associated with smaller LV size, lower stroke volume, and lower cardiac output, without changes in LVEF(28). These findings may possibly be explained by impaired ventricular filling resulting from hyperinflation, which can be seen even in early obstructive disease with loss of lung parenchyma and capillary beds. The reduction of pulmonary vein cross sectional area in COPD and emphysema may contribute to LV underfilling(29). For example, among ever smokers without lung disease, lower pulmonary vascular volume was associated with lower LV filling, without impact on LV relaxation (30). In MESA-COPD study, the degree of hyperinflation was also associated with greater LV mass.(31) While advanced COPD has classically been associated with *cor pulmonale*, lesser degrees of COPD have actually been associated with reductions in RV size (‘cor pulmonale parvus’)(32). Loss of the pulmonary vasculature in COPD, and pulmonary arterial pruning in particular, appears to modify this association such that a greater loss of distal pulmonary arterial vasculature is associated with greater RV size for any given degree of emphysema(33). These findings highlight the complex interplay between airflow obstruction, parenchymal damage, pulmonary vascular remodelling, and cardiac structure and function in obstructive lung disease.

Less data are available regarding the association of restrictive ventilatory patterns, or restrictive lung disease, with cardiac structure and function. Existing data suggest robust associations with both LV diastolic dysfunction and RV dysfunction. For example, a small study with 26 cases of pure restrictive ventilatory impairment (percent predicted FVC ≤ 80% and FEV1/FVC above lower limit) showed a robust correlation of lower percent predicted FVC with greater right ventricle area ($r=-0.9$, $p<0.001$). However, frank RV enlargement and/or Doppler evidence of pulmonary hypertension was only observed in patients with moderate (percent predicted FVC 51-64%) and severe (percent predicted FVC ≤ 50%) restrictive ventilatory patterns. Those with only mildly reduced percent predicted FVC (percent predicted FVC 65-80%) demonstrated generally normal RV function(34). In the Gutenberg Health study, a population-based cohort with 15,010 individuals, lower FVC and percent predicted FVC were associated worsened diastolic indices (greater E/A and E/e’)

and with lower stroke volume and ejection fraction, in analyses adjusting for age, sex, BMI, diabetes, smoking, dyslipidemia and smoking(35).

Classic cor pulmonale is well described in the large group of restrictive ventilatory syndromes, especially in selected populations when vital capacity is severely reduced(36). Factors impacting the associated degree of RV and LV dysfunction include: direct immune or inflammation-mediated myocardial/vascular damage, as in autoimmunity (36); an indirect interplay between parenchymal and vascular damage, as in interstitial lung diseases (32, 33); or intermittent hypoxia and wide variations of sympathetic tone and intrathoracic pressure, as in obstructive sleep apnea/hypopnea(37). Interestingly, the association between reduced FVC and elevated CVD risk persists even after accounting for BMI and other metabolic/ inflammatory risk factors in non-selected populations, suggesting that subclinical interactions between pulmonary dysfunctions and CV risk are not fully explained by inflammatory or metabolic markers.

Impairments in FVC and FEV1/FVC ratio may also differentially promote alterations in cardiac structure and function. Among 3,000 participants in the CARDIA study, investigators related changes in spirometric measures over the first 20 years of the study to echocardiographic measures at study year 25 (mean age 50.2±3.5 years)(38). In models adjusted for age, race, sex, smoking, diabetes, greater decline in FEV1/FVC from early adulthood to middle age was associated with smaller LA size and lower cardiac output (‘small heart and low output’ phenotype) while greater decline in FVC was associated with greater LV mass, lower E/A ratio, and higher cardiac output (‘hypertrophic and high output’ phenotype) (38). It remains uncertain if these differences in LV remodelling phenotypes result in different risk of HF, or HF phenotype (e.g. HF with reduced ejection fraction vs HF with preserved ejection fraction).

Therefore, FVC decline with, versus without, proportional FEV1 decline likely represents distinct pathophysiologic processes, and differentially associates with alterations in cardiac function such that LV underfilling is observed in obstructive patterns and while greater LV mass and diastolic dysfunction are observed in restrictive patterns (17, 38). As RV dysfunction is typically a late manifestation of advanced pulmonary dysfunction, RHF would be unlikely in early stages irrespective of the spirometric pattern.

Pulmonary dysfunction has also been associated with subclinical atherosclerosis, though not consistently with coronary atherosclerosis. In MESA, an obstructive spirometric pattern was independently associated with greater carotid intima-media thickness (CIMT) and lower ankle-brachial index, especially among smokers. A restrictive spirometric pattern was not associated with either. Neither spirometric pattern was associated with the presence of coronary artery calcium (CAC) or with Agatson score(39). Similar findings were observed with younger participants from CARDIA, among whom FEV1 and FEV1/FVC decline were associated with CIMT after accounting for several confounders. FVC decline was not associated with CIMT and no measure was associated with CAC. These findings are consistent with the association of obstructive pattern and/or decline in FEV1 with incident stroke, but not with coronary heart disease(17, 18).

Potential mechanisms linking pulmonary dysfunction with cardiovascular disease

While robust observational data demonstrate associations between clinical and subclinical pulmonary and cardiac dysfunction independent of common risk factors, the responsible mechanisms are yet to be defined. Clearly regression models do not entirely represent the biological complexity of shared risk factors impacting lung and heart health. Inflammation is perhaps the most prominently cited shared risk factor. FEV1 is inversely related to C-reactive protein (CRP) in early adulthood(40). Elevated inflammatory markers (CRP and fibrinogen) in young adults also associate with a greater 15-year decline in FEV1 and FVC(41). Associations have also been identified between longitudinal changes in FEV1 and FVC and circulating levels of adhesion molecules such as ICAM and P-selectin that persist after adjusting for clinical characteristics and comorbidities (42). Notably, while these relationships were independent of smoking, the magnitude of association tended to be higher among smokers, supporting a bidirectional relationship between inflammation and lung dysfunction.

Inflammation is also implicated in the development of cardiovascular diseases, particularly atherosclerotic disease (43), as highlighted by the efficacy of canakinumab, an anti-IL-1β monoclonal antibody, for the prevention of atherosclerotic events in the CANTOS trial(44). Inflammation is also a proposed mechanism underlying LHF, including HF with preserved ejection fraction (45), to which lung dysfunction is an important contributor (46).

Inflammation is the most accepted theory linking pulmonary and cardiovascular diseases. Individual predisposition combined with continuous or intermittent insults (e.g. smoking, air pollutants, infection) could trigger a subclinical inflammatory state – both local and systemic – resulting in simultaneous impairment in both pulmonary and cardiovascular functions(47). Indeed, the immune spill-over hypothesis posits that pulmonary inflammation may drive a systemic inflammatory state impacting other organs, although data supporting this theory are limited (48). Specific inflammatory pathways have not been fully elucidated and there is no evidence to-date that therapies targeting inflammation mitigate pulmonary disease-associated cardiac dysfunction.

The association of inflammation with cardiac function is best described for LV dysfunction, while little is known about the direct impact of inflammation on RV function and associated RHF.

Clinical Implications

Cardiovascular and pulmonary diseases commonly co-exist. Despite established associations with subclinical and clinical lung dysfunction, spirometry in patients with cardiovascular disease is underutilized. In two large registries of HF patients, less than 50% of chronic LHF patients with COPD had spirometric data.(49, 50). Although spirometry interpretation may be challenging within the context of concomitant LHF, these data suggest that only a minority of LHF patients with COPD undergo confirmatory pulmonary function evaluation, which is useful for diagnosis, stratification and appropriate treatment.

Management challenges also exist for patients with concomitant cardiac and pulmonary disease (mostly COPD). Patients with concomitant COPD are less likely to receive ACE inhibitors and beta-blockers, especially among hospitalized LHF patients(49). Safety concerns with use of beta-blockers in patients with COPD contributes to their underuse in hospitalized patients (49, 50) and outpatients (51), although the evidence suggests that especially beta-1 receptor antagonists are generally safe(52, 53) and that their beneficial effects persist even in severe COPD patients (54). On the other hand, inhaled bronchodilators can increase heart rate and myocardial oxygen consumption, and may worsen outcomes in patients with LHF and coronary artery disease (55). Short acting inhaled beta-mimetics are associated with increased risk of LHF hospitalization (50), therefore should be avoided. Long acting muscarinic antagonists (LABAs) are the mainstay treatment for COPD (56) and may be also preferred in patients with concomitant LHF(57). A small (n=40) randomized crossover trial showed that in selected patients with HFrEF (NYHA I-II) and mild/moderate COPD, inhaled tiotropium for 28 days was associated with a short-term improvement in LVEF and BNP levels (58). Although generally safe, LAMAs should be used cautiously, especially with more advanced LHF (55).

Limited data are available regarding restrictive lung diseases. For ILDs, the overall recommendation is to treat the underlying lung disease. Prior studies have not demonstrated improvements in symptoms or prognosis with PAH-directed therapies (36). While immunosuppression is the mainstay of ILD therapy, it is not known whether such therapies provide direct or secondary cardiovascular benefits in this context (37).

The therapeutic goal is to optimize the evidence-based treatment for each disease individually, although robust evidence regarding the overlap of concomitant cardiac and pulmonary diseases is absent. Interventions that clearly effectively benefit both diseases include smoking cessation, influenza and pneumococcal vaccination, and physical activity for primary prevention or rehabilitation(59).

Conclusion

The deleterious interaction between pulmonary and cardiovascular disease is well recognized and has significant impact in morbidity, mortality and quality of life. A growing body of evidence from longitudinal studies has shown that:

1. Before the development of clinically diagnosed pulmonary disease, subclinical decline in lung function represented by spirometric variables - FEV1, FVC and FEV1/FVC ratio – are associated with increased risk of general and cardiovascular death, and of incident CVD such as LHF, AF and stroke, independently of traditional risk factors. These associations are particularly strong for restrictive spirometric patterns.
2. An early onset and the rate of decline in lung function further increase CVD risk.
3. Associations of pulmonary function with coronary artery disease are more modest and largely attenuate after accounting for other common risk factors.

4. The most promising underlying mechanism that bridges lung and heart dysfunction is chronic systemic inflammation. However, lung dysfunction is also associated with hypertension, increased adiposity, and metabolic syndrome, all of which are risk factors for CVD.

While the management of patients with co-morbid pulmonary and cardiovascular disease is challenging, opportunities exist for improvement. Future directions may include: (1) better characterization of pulmonary function (and dysfunction) in cardiovascular patients using readily available tools such as spirometry; (2) avoidance of underprescription of effective evidence-based therapies for each condition; (3) greater collaboration between pulmonology and cardiology specialists to individualize treatment; (4) in the research field, better understanding the common inflammatory pathways and susceptible genotypes/phenotypes to identify potential therapeutic targets for associated cardiopulmonary dysfunction.

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TABLE:

Key studies addressing the clinical and subclinical relationships between pulmonary and heart function.

Reference	Study type	Associations
Chen et al (2015)(4)	Systematic review (89 references) and Metanalysis (29 references) mostly observational studies comparing COPD patients to non-COPD population.	- COPD patients are more likely to be diagnosed with: -Any cardiovascular disease: OR 2.46; 95% CI 2.02-3.00; - Coronary artery disease: 2.28; 1.76-2.96; -Arrhythmias: 1.94; 1.55-2.43 including atrial fibrillation; - Heart failure: 2.57; 1.90-3.47; - Diseases of the pulmonary circulation (acute or chronic pulmonary heart disease, pulmonary embolism, and *cor pulmonale*: 5.14; 4.07-6.50. - COPD patients had greater likelihood to have hypertension (1.33; 1.13-1.56), diabetes (1.36; 1.21-1.53) and ever smoking (4.25; 3.23-5.60).
Sidney et al (2005)(6)	Observational study from the Kaiser Permanente Medical Care program, that enrolled 45,966 patients with COPD and compared CVD outcomes with an equal number of controls, matched for gender, birth year and length of membership.	- COPD was associated with a greater risk of CVD hospitalization and mortality in an average follow up of nearly 3 years, independently of age, gender, hypertension, dyslipidemia and diabetes, after excluding those prevalent CVD at baseline. Highest rate ratios (RR) for hospitalization were: - Heart Failure: RR 3.85; 95% CI 3.44–4.32; - VT/VF/cardiac arrest: 2.78; 1.75, 4.42; and - Pulmonary embolism: 2.74;1.99–3.76. Highest mortality rate ratios were: - Heart Failure: RR 3.50; 2.22–5.50; and - Myocardial infarction: 1.85; 1.55–2.21.
Johnston et al (2008)(9)	Observational study of 14681 participants from ARIC cohort to determine the association between lung function impairment with prevalent and incident CVD at baseline and over 15 years of follow-up	- Compared to participants with a normal spirometry, restrictive spirometric pattern showed the highest magnitude of association with CVD at baseline (OR 3.4, 95%CI 2.8-4.2), which persisted even after accounting for several risk factors and covariates (adjusted OR 2.3, 95%CI 1.9-2.9). - In participants free from CVD at baseline, restrictive spirometric pattern was associated to an increased risk for incidental CVD (adjusted HR 1.4, 95%CI 1.02-1.9), when compared to participants with a normal spirometry.
Cuttica et al (2018)(17)	Observational study of 4761 young participants (18-36 years) from CARDIA cohort to determine the association between lung health in young adulthood and risk of subsequent cardiovascular events over 29 years of follow up	- Lower percent predicted FEV1 (adjusted HR 1.18; 95%CI 1.06) and FVC (1.19; 1.06-1.33), but not FEV1/FVC ratio (1.03; 0.93-1.14), was associated with greater risk of the composite of fatal and non-fatal cardiovascular events independent of age, gender, race, education, baseline body mass index, smoking, diabetes, systolic blood pressure, use of anti-hypertensive medication, total and HDL-cholesterol. - Worse FVC in particular was also independently associated with greater risk for incident left heart failure (1.29; 1.03-1.62), while percent predicted FEV1 (1.20; 0,98-1.48) and FEV1/FVC ratio (0.93; 0.75-1.16) were not.
Cuttica et al (2015)(38)	Observational study of 3000 young participants from CARDIA cohort to determine the association between lung health in young adulthood and cardiac structure and function over 20 years of follow up	- Decline in FVC (peak – year 20; mean 40mL/year in men and 33mL/year in women) was associated with larger left ventricular mass, greater cardiac output and diastolic dysfunction. - Decline in FEV1/FVC ratio (mean 0.30/year in men and 0.37/year in women) was associated with smaller left atrial internal dimension and lower cardiac output.
Silvestre et al (2018)(18)	Observational study of 10,351 participants from ARIC cohort to evaluate whether longitudinal decline in lung function in 2.9 years is associated with incident heart failure, coronary heart disease, and stroke over 17 years of follow up	- Rapid decline in FEV1 (reduction in >1.9% per year) and in FVC (decline in >2.1% per year) were both associated with a heightened risk of incident HF (HR 1.17; 95% CI 1.04-1.33; and 1.27; 1.12-1.44 respectively), with rapid decline in FEV1 most prognostic in the first year of follow-up (4.22; 1.34-13.26). - Rapid decline in FEV1 was also associated with incident stroke (1.25; 1.04-1.50). - These associations were independent of age, gender, race, height, ARIC center, body mass index, heart rate, low-density lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking.
Barr et al (2010)(28)	Observational study of 2816 participants from MESA cohort to evaluate the association of emphysema and airflow obstruction, from CT and spirometry, with cardiac structure and function, from MRI	- A 10-point increase in percent emphysema was linearly related to reductions in left ventricular end-diastolic volume (−4.1 mL; 95%CI −3.3 to −4.9; p<0.001), stroke volume (−2.7 mL; 95%CI −2.2 to −3.3; p<0.001), and cardiac output (−0.19L/min; 95%CI −0.14 to −0.23; p<0.001). - Percent emphysema and airflow obstruction were not associated with the left ventricular ejection fraction.

COPD: chronic obstructive pulmonary disease; OR: odds ratio; CI: confidence interval; RR: rate ratio; CVD: cardiovascular disease; VT/VF: ventricular tachycardia/fibrillation; ARIC: Atherosclerosis Risk in Communities study; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; CARDIA: Coronary Artery Risk Development in Young Adults; MESA: Multi-Ethnic Study of Atherosclerosis; CT: computed tomography; MRI: magnetic resonance imaging.