Cardiac disease from accelerated FEV_1 decline and acute exacerbations: time to rethink comorbidities in COPD

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COPD is a prevalent disease in middle-aged and older adults associated with significant morbidity and mortality [1]. Individuals with COPD have an increased risk of different comorbidities, which complicates management of an already troublesome disease [2, 3]. One of these comorbidities is cardiovascular disease, which is believed to arise from shared risk factors, such as tobacco smoke, and the higher prevalence of major cardiovascular risk factors in individuals with COPD [4]. Nonetheless, even after accounting for all these risk factors, there remains an association between COPD and cardiovascular disease suspected to involve such diverse mechanisms as hypoxia and systemic inflammation [4].

It is now increasingly evident that airflow limitation in COPD develops gradually over many years from different lung function trajectories [5]. So far, we have been able to identify two of these lung function trajectories; that is, acceleration of the normal age-related decline of lung function due to exposure to noxious particles or gases such as tobacco smoke, and low maximally attained lung function in early adulthood [6–8]. However, lung function trajectories not only seem to have an importance for the development of airflow limitation in COPD but also prognosis and risk of comorbidities afterwards. Recently, it was shown that COPD developed through accelerated lung function decline is associated with a higher mortality rate compared to COPD developed through low maximally attained lung function in early adulthood [9]. In addition, low maximally attained lung function in early adulthood has been associated with development of cardiovascular and metabolic disease later in life [10]. An obvious question therefore arises: whether the linkage between COPD and comorbidities such as cardiovascular disease could partly be explained by pathogenic mechanisms responsible for airflow limitation?

In this issue of the *European Respiratory Journal*, Whittaker *et al.* [11] address the question whether accelerated lung function decline is associated with increased cardiovascular disease in patients with COPD from a primary care population in England. By using the Clinical Practice Research Datalink, an electronic healthcare database of a subset of general practitioners (contains 7% of the UK population),

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approximately 36 000 patients with COPD were included. Patients with COPD were initially followed for at least 3 years to estimate forced expiratory volume in the first second (FEV_1) decline, and hereafter followed for up to 10 years to estimate risk of coronary heart disease, heart failure, myocardial infarction, stroke, atrial fibrillation and cardiovascular mortality. Accelerated FEV_1 decline was defined as patients with the steepest quartile of the decline, corresponding to approximately >40 mL per year. During follow-up, more than 6000 patients developed or died due to cardiovascular disease. After a careful analytical approach, the investigators did not find evidence of an association between accelerated FEV_1 decline and risk of cardiovascular disease or mortality in patients with COPD. Compared to patients with non-accelerated FEV_1 decline, adjusted hazard ratio for composite cardiovascular disease was 0.98 (95% CI 0.90–1.06) in those with accelerated FEV_1 decline. Corresponding hazard ratios were 1.02 (95% CI 0.87–1.19) for coronary heart disease, 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 0.83–1.23) for stroke, 0.97 (95% CI 0.81–1.15) for atrial fibrillation and 0.94 (95% CI 0.71–1.25) for cardiovascular mortality, respectively.

These results are of considerable interest, as they illustrate for the first time that accelerated FEV_1 decline, a major pathogenic mechanism in development of airflow limitation, is not associated with excess cardiovascular comorbidity risk in patients with COPD. Instead, Whittaker *et al.* [11] found that frequency and severity of acute exacerbations and increased breathlessness, as measured by the modified Medical Research Council Dyspnoea scale (mMRC), increased cardiovascular comorbidity risk independent from major risk factors. In fact, the risk estimates for acute exacerbations sometimes seemed higher than other traditional risk factors, including tobacco smoke, body mass index, diabetes and hypertension (tables E1–E7 in the supplementary material of [11]). While mMRC may be rather unspecific and could in principle be sign of underlying coronary artery disease, acute exacerbations have previously been associated with increased risk of cardiovascular disease [12, 13]. A *post hoc* analysis of the SUMMIT trial showed that risk of major cardiovascular disease events, including myocardial infarction, stroke and cardiovascular mortality, was substantially increased within 30 days from a subsequent acute exacerbation in patients with COPD and even persisted up to 90 days and to 1 year [14]. The risk was highest for those exacerbations requiring hospitalisation [14]. Similarly, in the UPLIFT trial, subsequent acute exacerbation increased risk of myocardial infarction and stroke [15]. Thus, there now seems to be substantial evidence to suggest that patients with COPD need to be followed closely for cardiac events following an acute exacerbation. But the real question is, can we prevent them and with which intervention? A potential mechanism that has been proposed includes elevated inflammatory biomarkers in blood during and after an acute exacerbation, thereby leading to systemic inflammation [14, 16, 17]. This could be plausible as systemic inflammation through the interleukin-6 signalling pathway has been causally linked to coronary heart disease [18, 19], and modulation of it with canakinumab seems to reduce cardiovascular event rates [20].

Interestingly, these results presented by Whittaker *et al.* [11] contrast with the recent findings in the Atherosclerosis Risk in Communities (ARIC) cohort, a general population sample from USA, where accelerated FEV_1 decline was associated with increased risk of heart failure in approximately 10 000 individuals [21]. The reason for the discrepancy may be differences in study design, including length of follow-up time, cohorts from different time periods, and how endpoints were assessed. However, it may also be that the importance of the FEV_1 decline differs before and after development of COPD. While accelerated FEV_1 decline may increase risk of certain cardiovascular diseases in individuals without COPD, it probably has less importance in individuals with COPD and is overshadowed by other risk factors such as acute exacerbations. Unfortunately, Whittaker *et al.* [11] were unable to explore this association in individuals with normal spirometry.

Strengths of the present study include an impressive large primary care population of COPD patients with a long follow-up time on wide range of different cardiovascular diseases identified from valid sources. An important limitation, also acknowledged by the investigators, is that patients with COPD were required to have at least 3 years of follow-up to estimate FEV_1 decline, which may lead to some form of immortal time bias, *i.e.* that patients had to survive until estimation of the decline before they could be included and were potentially "immortal" during this time period. Another limitation is that FEV_1 decline was only determined for a very short time period, which would be more accurate if a longer time period was used instead. Another limitation is the lack of other important potential confounders such as tobacco consumption, plasma cholesterol, physical activity and alcohol consumption; however, it is reassuring to see that risk estimates were largely similar in unadjusted and adjusted analyses, suggesting a low impact of residual confounding. Risk estimates were also largely similar in extensive subgroup and sensitivity analyses, suggesting that results are likely robust and valid.

Comorbidities in COPD are often explained by shared risk factors, which therefore need to be considered, prioritised, handled and treated accordingly. However, shared risk factors do not completely explain the very high burden of comorbidities in COPD, where we sometimes need to use different, and often

unconventional, ways to study and understand them. In recent years, we have started to focus again on the natural history of airflow limitation in order to understand COPD heterogeneity. Perhaps lung function trajectories can be extended beyond COPD to explain the interplay between health and disease [22]. With their study, WHITTAKER *et al.* [11] should be congratulated for helping us to understand cardiovascular comorbidity risk further in patients with COPD.

Conflict of interest: Y. Çolak reports personal fees from Boehringer Ingelheim, AstraZeneca and Sanofi Genzyme outside the submitted work.

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