Airway inflammation is associated with reduced lung function. With progressive loss in lung function, the inflammatory process intensifies. Individuals with increased airway inflammation have a faster decline in lung function, leading to the development of chronic airway diseases such as chronic obstructive pulmonary disease (COPD). Once COPD is firmly established, the airways become more vulnerable to additional damage, leading to a further deterioration in lung function, which in turn becomes a substrate for more inflammation. The only known therapy that can mitigate this process is smoking cessation.

Although it has been recognized for more than 30 years that airway inflammation plays a central role in COPD progression (and reduction in lung function), the potential importance of systemic inflammation has not been fully appreciated until quite recently. Systemic inflammation is present in individuals with reduced lung function, as assessed by forced expiratory volume in 1 s (FEV₁) and the intensity of systemic inflammation varies inversely along the FEV₁ gradient. In those with reduced lung function, systemic inflammation has been implicated with a variety of poor clinical outcomes.
including cardiovascular diseases, peripheral muscle dysfunction, and even all-cause mortality.5

The study by Thyagarajan et al.7 in this issue of the International Journal of Epidemiology highlights another potential role of systemic inflammation: it may be involved in the pathogenesis of chronic lung disorders. The investigators used data from participants of the Coronary Artery Risk Development in Young Adults (CARDIA) Study, who provided plasma samples at years 5 and 7 and who performed spirometric manoeuvres during these visits as well as an extra visit in year 10. The baseline lung function and plasma fibrinogen levels were available in 4040 participants (mean age 30 years). Using this cohort, the investigators made several interesting and important observations. First, cross-sectionally, reduced lung function was significantly related to plasma fibrinogen levels, a marker of systemic inflammation. The FEV1 of subjects in the lowest quartile of fibrinogen (<6.5 μmol/l) was 4.6% higher compared with those in the highest quartile (>8.6 μmol/l). Second, the plasma fibrinogen level at year 5 was significantly related to lung function in year 10. The excess decline in FEV1 associated with elevated fibrinogen was in the order of 15 ml/year, a magnitude that was as large if not larger than the effects of intermittent smoking cessation on lung function.4 Collectively, these data raise the possibility that systemic inflammation, and in particular fibrinogen, may accelerate lung function decline in young adults and predispose them to airway diseases such as COPD in the future.

There were many strengths to the present study. CARDIA was a population-based sample of young adults largely devoid of any major illnesses or medications that could have influenced lung function. Additionally, the investigators collected a lot of baseline and follow-up information on important demographic and clinical parameters, which allowed them to carefully adjust for potential confounding factors using well-accepted modelling procedures. The most important potential confounder was cigarette smoking, which by itself induces systemic inflammation and is a known (and arguably the most salient) risk factor for reduced lung function.5 It was assuring that even in the subgroup who did not smoke, the relationship between plasma fibrinogen and lung function held indicating that this process was not confounded by cigarette smoking.

However, there were some limitations to this study. While it may be that systemic inflammation caused the reduction in lung function, the possibility of reverse causation could not be ruled out. Moreover, because the present study did not evaluate any lung markers of inflammation, it is not certain whether systemic inflammation was a primary or secondary response to local inflammation in the lungs. Although plasma fibrinogen is a robust and reliable marker of systemic inflammation, hepatic production of fibrinogen can occur through inflammation-independent pathways (e.g. use of oral contraceptives).6 Measurements of other inflammatory molecules would have strengthened the findings. Finally, it is not clear, based on this study, whether fibrinogen is intrinsically involved in FEV1 reduction or an epiphenomenon of other systemic molecule(s) that are responsible for lung remodelling. There are animal models that suggest that fibrinogen may be an important effector molecule in airway disease. For instance, fibrinogen in the lungs can (i) inactivate pulmonary surfactant, causing increased surface-tension relationships in the distal airways, (ii) promote the expression of molecules that induces airway fibrosis and narrowing, and (iii) activate plasminogen activator inhibitor type-1 leading to excess fibrin deposition in the airways and airway narrowing.10 These properties of fibrinogen suggest that it is more than an epiphenomenon; rather it is involved in the causal pathways.

Notwithstanding these limitations, the present study has added materially to the current understanding of the role that systemic inflammation plays in lung disorders. First, the present study has shown a significant relationship between plasma fibrinogen and accelerated decline in lung function in young adults. If this trend continues into later years of life (and there is no compelling reason to think otherwise), logically, elevated plasma fibrinogen levels should be an important risk factor for COPD. Indeed, that appears to be the case. Dahl and co-workers showed that the risk of COPD hospitalization increases by 70% in individuals with elevated plasma fibrinogen levels11 and for every 1 g/l increase in plasma fibrinogen, the future risk for COPD mortality increases nearly 4-fold.12 Thus, the present study provides a physiological rationale (i.e. accelerated decline in FEV1) for the epidemiological association between fibrinogen and COPD hospitalization and mortality that have been previously observed. Second, the present study provides a solid rationale for targeting systemic inflammation and in particular plasma fibrinogen and interleukin-6, which is the primary cytokine responsible for signalling hepatic synthesis of fibrinogen, to attenuate future risk of COPD hospitalization and mortality in the at-risk populations.9 Third, these findings suggest that plasma fibrinogen can be used, in addition to traditional risk factors such as age, smoking and gender, to risk-stratify young individuals in the community for future risk of COPD and to implement interventions such as smoking cessation and perhaps anti-inflammatory medications to modify that risk in such individuals.

In sum, the study by Thyagarajan provides added fuel to a growing body of literature indicating the importance of systemic inflammation in chronic lung disorders and will stimulate additional research to determine the precise mechanisms involved in this process. Hopefully, such targeted research will lead to novel therapeutic discoveries to combat the global epidemic of COPD and its related disorders that are projected to materialize within the next decade.13

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