Chronic obstructive pulmonary disease (COPD) is currently the 4th leading cause of death worldwide. Although COPD has a heterogeneous clinical presentation, it is primarily characterized by airflow limitation and is generally associated with an abnormal inflammatory response of the lungs. It is also often associated with a significant systemic inflammatory response, which has been correlated with adverse clinical events. Over the past decade, there has been increased interest in the link between respiratory disease and cardiovascular disease (CVD). CVD is the major cause of mortality and morbidity in patients with COPD, and nearly 33.6% of patients with COPD have coronary artery disease.

B-mode ultrasonography is a noninvasive and readily available imaging modality for the measurement of the carotid intima-media thickness (IMT), which is now widely used as an adjunct to traditional cardiovascular risk factors to assess atherosclerotic burden. Indeed, several cross-sectional studies have demonstrated an association between carotid IMT and the severity of atherosclerosis in the coronary arteries, cerebrovasculature, abdominal aorta and femoral arteries. Furthermore, a prospective study has shown an association between carotid IMT and the incidence of events related to coronary artery disease and stroke.

In this issue of the Journal, Kudo et al. report how they estimated airflow from the flow-volume curve (FEV1/FVC)
and measured carotid IMT by B-mode ultrasound. They show that airflow limitation (FEV1/FVC <70%) as the standard definition of COPD by the Global Initiative for Chronic Obstructive Lung Disease was closely associated with carotid artery thickening, especially in middle-aged subjects, in the Hisayama Study. The main intent was initially to describe the health and disease status of the community. Hisayama is unique because it has maintained traditional agricultural practices, resisted industrialization and remained a stable population compared with communities in other Japanese regions. Hisayama has a male-female ratio and age distribution that are similar to the national average. The most impressive aspect of Kudo et al’s report is that the relationship between COPD and atherosclerosis was verified in a large sample (n=2,099) of the Japanese general population.

In Japan, approximately 5.3 million and 8.6% of the population over 40 years old have COPD. According to a survey by the Ministry of Health, Labor and Welfare in 2014, the number of patients in hospitals diagnosed with COPD was approximately 260,000. This means there are more than 5 million people who have COPD but are not being treated for this disease. Many people might not be aware that they have COPD or might not have been diagnosed correctly. The greatest cause of COPD is smoking, and 15–20% of smokers develop COPD. According to the 2015 statistics of the Japan Ministry of Health, Labor and Welfare, the proportion of current smokers in the general population is 30.1% in men and 7.9% in women. The overall smoking rate is 18.2%. Looking at the trend from 2003, the overall smoking rate has shown a moderate decline; there was an increase in the smoking rate in women but a decrease in men. However, with aging of the population, it is expected that the prevalence of COPD will increase in Japan in the future.

Kudo et al show an association between COPD and carotid atherosclerosis after adjusting for a smoking habit. Their data show that smoking is the primary cause of COPD and atherosclerosis, but COPD itself is the primary cause of atherosclerosis. However, the mechanisms responsible for the association between COPD and atherosclerosis are still largely unknown. As mentioned by Kudo et al, some important factors are hypoxia, local inflammation, systemic inflammation, oxidative stress and hypercoagulation caused by platelet activation.

Patients with COPD are subject to hypoxia, either sustained in patients with severe disease or intermittent during exercise or symptom exacerbation. When cellular oxygen availability decreases, the transcription factor, hypoxia-inducible factor 1 (HIF-1), plays a central role in hypoxic cellular adaptation. HIF-1 induces the expression of several angiogenic factors, including vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase and platelet-derived growth factor. Enhanced expression of HIF-1 and VEGF is strong evidence that in the development of atherosclerosis, endothelial cells proliferate and form vessels under hypoxic stimuli. Vascular smooth muscle cell (VSMC) proliferation and migration in response to vascular injury contribute to vessel narrowing and play an important role in the atherosclerotic process.