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Reduced Lung Function in Midlife and Cognitive Impairment in the Elderly

In recent years, the interpretation of respiratory diseases has shifted from localized entities to single components of systemic multimorbidities (1, 2). Respiratory diseases were first linked to cardiovascular and metabolic diseases (3, 4) and later also to cognitive disorders (5).

In a study presented in this issue of the *Journal*, Lutsey and colleagues (pp. 1385–1396) used a community-based cohort enrolled within the framework of the ARIC (Atherosclerosis Risk in Communities) study (6) to address the association between respiratory and neurological disorders (7). They found that "both restrictive and, to a lesser extent, obstructive lung disease were associated with greater risk of incident dementia and mild cognitive impairment (MCI)" after a 27-year follow-up. Lung function parameters (FEV_1% predicted and FVC% predicted) were significantly associated with cognitive impairment due to both Alzheimer's disease and cerebrovascular disease, although the latter association was much stronger than the former (Tables 4 and 5 in Reference 7).

The present results confirm and enlarge the findings of a previous longitudinal ARIC study (5), which found that a restrictive ventilatory pattern, but not an obstructive pattern, was associated with reduced cognitive scores and a higher risk of hospitalization for dementia. The present study, using a longer follow-up and also including patients with stroke or coronary artery diseases, managed to show that a restrictive pattern was associated with cognitive impairment 27 years later, and that an obstructive pattern also significantly affected cognitive status, although to a lesser extent. Of note, the two studies used different cutoffs to define airways obstruction: a fixed FEV_1/FVC ratio of 0.70 in the previous study (5), and the lower limit of normal in the present study. Interestingly, the latter classification has been shown to select more severe cases of airways obstruction in the elderly (8).

Both ARIC studies support the notion that a restrictive pattern plays a stronger role than an obstructive pattern in cognitive impairment. In agreement with current literature (9), the restrictive pattern was strongly associated with all of the features of metabolic syndrome in the current study: at baseline, subjects with a restrictive pattern had a mean body mass index of 30.3, 36.2% were treated with antihypertensive medications, and 22.4% had diabetes, and they had lower high-density lipoprotein cholesterol and higher low-density lipoprotein cholesterol than the other subjects. In a multivariable analysis, the association between restrictive impairment and dementia/mild cognitive impairment persisted even after adjustment for 15 well-known cardiovascular risk factors, although the odds ratio (OR) decreased from 1.92 (95% confidence interval [CI], 1.40–2.63) to 1.56 (95% CI, 1.12–2.16) (Table 3 in Reference 7). This suggests that the relation between restrictive pattern and cognitive impairment is partly mediated by metabolic/cardiovascular comorbidities. On the other hand, the strength of the association between obstructive pattern and cognitive impairment was much weaker (OR, 1.30; 95% CI, 1.07–1.60), but remained unchanged when adjusting for the same cardiovascular risk factor (OR, 1.31; 95% CI, 1.06–1.62).

The authors adopted an interesting study design by integrating information from administrative databases with information from an *ad hoc* comprehensive neurocognitive exam. The use of administrative databases allowed the authors to study the

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whole cohort ($n = 14$, 184 subjects), but such databases lack sensitivity with respect to hospitalization and death from dementia, as acknowledged by the authors. Of note, respiratory diseases are difficult to identify through administrative databases: in an Italian study (10), the sensitivity was 53% for chronic obstructive pulmonary disease (COPD) and even lower (39%) for asthma. Indeed, the association between lung diseases and incident dementia, identified by hospitalization diagnosis codes, was not significant after adjusting for smoking, and among lung function parameters, only FVC% presented a borderline significant association with incident dementia after adjusting for cardiovascular risk profile (Table 2 in Reference 7).

Conversely, the *ad hoc* follow-up survey suffered from low participation (42%), which was mostly due to the fact that 36.7% of the participants died during the follow-up. Interestingly, participants and nonparticipants who were still alive had similar baseline characteristics, and largely differed from the deceased subjects (Table E1 in the online supplement of Reference 7). The authors coped with potential selection bias in their multivariable analysis by adopting inverse probability weighting, where larger weights were assigned to subjects who were less likely to participate. The problem of low participation is not avoidable in longitudinal studies with long follow-up. Moreover, exposure–outcomes associations seem to be less affected by loss to follow-up than prevalence estimates (11).

The study by Lutsey and colleagues has some limitations regarding the baseline assessment of lung function and respiratory diseases, as acknowledged by the authors themselves. Indeed, bronchodilation was not used and TLC was not quantified. Due to these limitations, the authors adopted the expressions "restrictive impairment pattern" and "COPD pattern." However, although the causes of the obstructive pattern (asthma, chronic bronchitis, and emphysema) were investigated, the baseline assessment did not include potential causes of the restrictive pulmonary pattern, such as tuberculosis, pleural disease, pneumonia, and occupational dust exposure (silica and asbestos). It should be noted that bronchodilation and assessment of TLC, although required in the clinical setting (12), were seldom used in epidemiological studies performed in the 1980s. However, future epidemiological studies should consider assessment of postbronchodilation lung function (13) and TLC, at least in subsamples. Moreover, a recent ARIC study (14) showed that lung function decline assessed in the first year of follow-up was associated with an increased cardiovascular risk in the subsequent 20 years; the same approach could be used to study cognitive decline.

In conclusion, restrictive lung disease, and to a lesser extent obstructive disease, can be considered a predictor of cognitive decline. Cognitive impairment may further contribute to the risk of poor adherence to the management of respiratory disorders and nonpulmonary diseases. FVC, which was originally a measure of lung function, can be viewed as a nonspecific index of overall health, like body temperature, heart rate, and c-reactive protein. Further studies are needed to evaluate the combined effects of respiratory, cardiovascular, and metabolic diseases on cognitive decline. Loss to follow-up is not avoidable in longitudinal studies with decades of follow-up; nevertheless, possible selection bias must be addressed by comparing participants and nonparticipants, combining *ad hoc* surveys with administrative databases, and adopting innovative statistical methods. ■

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