Letters

COMMENT & RESPONSE

Cerebrovascular Disease and Sleep-Disordered Breathing Need to Be Accounted for in Cognitive Impairment Following COVID-19

To the Editor  Nersesjan et al1 report on cognitive and neuropsychiatric outcomes in COVID-19 survivors vs control individuals. Their study is a robust foray into the neurocognitive sequelae of COVID-19 that provides both follow-up and control data for comparison and context. However, there are 2 critical caveats that may impair generalizability: sleep-disordered breathing and cerebrovascular disease as drivers of cognitive impairment in both patients with COVID-19 and control individuals without COVID-19. The former caveat stems from screening that was not included in the authors measurements; the latter is a direct generalization of their results and may also imply other confounders, such as medication status.

A systematic review and meta-analysis in JAMA Neurology2 pooling 4 million participants denotes a 26% increase in risk of developing cognitive impairment and specifically executive dysfunction associated with sleep-disordered breathing compared with control individuals. Notably, dysexecutive syndromes also appear to manifest secondary to COVID-19, as another report indicates.3 Aside from its prevalence in the general population (ie, estimated as high as 17% of US adults4), sleep-disordered breathing and comorbidities, such as hypertension and cardiovascular disease, exhibit a bidirectional association.5,4 These comorbidities are among the control variables selected by Nersesjan et al,1 yet the presence of sleep-disordered breathing itself is not accounted for by the authors via formal measures. Potential sleep disturbances—only a single item—probes sleep disturbances in the authors sample but, defined as such, this variable relies on patients being aware of said sleep disturbance; it therefore cannot account for unconscious arousals that would otherwise disturb sleep architecture without being identified by the patient.

Aside from sleep-disordered breathing as a variable that has not been accounted for, the authors results from the limited number of participants who underwent magnetic resonance imaging (ie, 5 patients with COVID-19 and 4 control individuals) indicate that 4 of 5 patients with COVID-19 exhibited cerebrovascular disease and hydrocephalus that could, on their own, account for secondary cognitive impairment.6 Furthermore, despite including participants without COVID-19 with small vessel disease and stroke risk factors (ie, hypertension and cardiovascular disease), there was little evidence of structural brain damage in that group. This could be because of low sample size, the protective effect of agents already administered for such disease (eg, statins, antiplatelets, or anticoagulants), or both. It also presents a critical limitation for the generalizability of the authors conclusions: if the effects uncovered by their analysis are primarily vascular, abortive medication should also be a control variable. If this is a batch effect, it should be attributed as a limitation. Notably, specific natural history trajectories for cognitive impairment secondary to stroke may also be evident in the authors follow-up data.5

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