Title

Reply to: Self-reported olfactory loss in COVID-19: is it really a favorable prognostic factor?

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REPLY to "Self-reported olfactory loss in COVID-19: is it really a favorable prognostic factor?"

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REPLY to "Self-reported olfactory loss in COVID-19: is it really a favorable prognostic factor?"

To the Editor,

The authors would like to thank our colleagues at Guys and St Thomas' Hospital and the University Hospital of Sassari for highlighting our study in their letter to the editor titled "Self-reported olfactory loss in COVID-19: is it really a favorable prognostic factor?" It is with great interest and appreciation that we have been watching the psychophysical olfactory data being published on COVID-19-related olfactory dysfunction. We commend all who continue actively contributing to our understanding of this pandemic.

We have previously reported a strong association between self-reported anosmia and 'mild' (outpatient) disease as compared to 'moderate' / 'severe' (inpatient) disease, that is independent of other markers of disease severity (chest x-ray findings, vitals at time of COVID-19 testing).[1] As noted, we were indeed concerned with the possibility of recall bias in patients with more severe disease, and therefore recommended that further investigation of larger, multi-institutional, epidemiologically generalizable cohorts using longitudinal psychophysical testing would be required

to validate our findings. Importantly, we suggested that anosmia would represent an important marker of disease prognosis only if our findings were reproducible in such studies.

Hopkins and colleagues' critique of our data centers on two inter-related points: (1) recall bias with underreporting of smell loss in sicker patients experiencing respiratory distress that (2) would otherwise be detected by psychophysical testing. In other words, that severe respiratory distress is inversely correlated with self-reported anosmia. In determining our study design, we shared a similar concern and therefore built an *a priori* multivariable logistic regression model to include subjective and objective variables associated with respiratory distress: age, dyspnea, presenting respiratory rate, temperature, and chest radiograph findings. Self-reported smell loss did not correlate with respiratory distress by these metrics, and olfactory loss was independently and inversely correlated with hospital admission (OR: 0.09, 95% CI 0.01 -0.74, p <0.025). Consistently, evaluation of clinical factors associated with self-reported smell loss confirmed hospital admission as the only variable independently related to olfactory dysfunction.

At the time of our study's writing, only one study had reported COVID-19-related quantitative olfactory testing, specifically only in an inpatient cohort.[2] While objective olfactory dysfunction was ubiquitous in this cohort (97%), self-reported olfactory loss was significantly lower (35%). Therefore, we noted a suspicion that this difference was related to severity of chemosensory dysfunction. Indeed, consistent with the incidence self-reported smell loss in our inpatient cohort, Moein and colleagues found that only 25% of their inpatient cohort experienced complete anosmia. As our study suggested, milder cases of COVID-19 may be heralded by profound anosmia and higher self-reporting, compared to the undetected or lesser degrees of hyposmia associated with moderate to

severe COVID-19 cases. This might explain why other reports of outpatient/mild or inpatient/severe COVID-19 cohorts, although anamnestic and self-reported, tend to support our findings.[3–5]

In their letter, Hopkins and colleagues felt that the recent psychophysical olfaction data that they collected were incongruent with our self-reported findings.[6] However, in reviewing their findings, we note that patients with mild disease have more severe quantitative olfactory dysfunction compared to those with moderate disease (mean olfactory score 54.5 vs. 64.5). Thus, one may logically infer that in their cohort while mild, moderate, and severe patients all experience some level of olfactory dysfunction, the severity of the objective olfactory loss may ultimately drive a patient's self-reported chemosensory experience. In fact, the objective data presented by Vaira et al could potentially be construed as supportive of our theory that milder cases of COVID-19 are associated with higher rates of self-reported olfactory loss.

Notably, Vaira and colleagues' determination that patients with chemosensory dysfunction longer than 7 days are at a higher risk of developing severe symptoms is also based on self-reported data. These results lack multivariable adjustment to determine whether length of olfactory dysfunction independently associates with disease severity. Importantly, the suggestion that duration of olfactory dysfunction may be associated with increased disease severity is not mutually exclusive from our study, which suggested that the presence and severity of self-reported olfactory loss correlates with milder disease severity. We would encourage further research investigating both theories.

As amply emphasized in our prior report, there needs to be further research on COVID-19-related anosmia and its potential relationship to overall clinical course. Certainly, an isolated symptom in a single institution retrospective hypothesis generating study should not drive nuanced patient-centered clinical decision making.

We commend our colleagues for their research and for the opportunity to place our findings in the context of newly published, timely, and thoughtful investigations. In the end, we hope that dialogues such as these correspondences will lead us closer to clinically actionable truths. We look forward to more excellent work from all our colleagues on COVID-19-related olfactory dysfunction and eagerly anticipate future thoughts, data, and analyses on this topic.

Sincerely,

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