

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

To the Editor,

We 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 coronavirus 2019 (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; ie, 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 et al.'s critique of our data centers on 2 interrelated 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 (odds ratio [OR] 0.09; 95% confidence interval [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 1 study had reported COVID-19-related quantitative olfactory testing, specifically only in an inpatient cohort.² Although 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 et al.² 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 et al. felt that the recent psychophysical olfaction data that they had 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, although 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.⁶ 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 et al.'s⁶ 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

Correspondence to: Carol H. Yan, MD, Department of Surgery, Division of Otolaryngology-Head and Neck Surgery, University of California San Diego, 9350 Campus Point Drive, Mail Code 0970, La Jolla, CA 92037; e-mail: c1yan@health.ucsd.edu

Potential conflict of interest: A.S.D. is a consultant for Stryker endoscopy, Olympus, IntersectENT, Sanofi, and Optinose. The other authors have no financial disclosures.

Received: 8 May 2020; Revised: 8 May 2020; Accepted: 8 May 2020

DOI: 10.1002/alr.22606



View this article online at wileyonlinelibrary.com.

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,

Carol H. Yan, MD , Farhoud Faraji, MD, PhD ,
and Adam S. DeConde, MD

Department of Surgery, Division of Otolaryngology–Head and Neck
Surgery, University of California San Diego Health, La Jolla, CA

References

1. Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in COVID-19. *Int Forum Allergy Rhinol.* (821-831). Epub 24 April 2020. <https://doi.org/10.1002/alr.22592>. Accessed May 15, 2020.
2. Moein ST, Hashemian SMR, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: A biomarker for COVID-19. *Int Forum Allergy Rhinol.* (in press). Epub 17 April 2020. <https://doi.org/10.1002/alr.22587>. Accessed May 15, 2020.
3. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (in press). Epub 10 April 2020. <https://doi.org/10.1001/jamaneurol.2020.1127>. Accessed May 15, 2020.
4. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis.* (in press). Epub 26 March 2020. <https://doi.org/10.1093/cid/ciaa330>. Accessed May 15, 2020.
5. Menni Cristina, Valdes Ana M., Freidin Maxim B., Sudre Carole H., Nguyen Long H., Drew David A., Ganesh Sajaysurya, Varsavsky Thomas, Cardoso M. Jorge, El-Sayed Moustafa Julia S., Visconti Alessia, Hysi Pirro, Bowyer Ruth C. E., Mangino Massimo, Falchi Mario, Wolf Jonathan, Ourselin Sebastien, Chan Andrew T., Steves Claire J., Spector Tim D.. Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nature Medicine.* 2020; <https://doi.org/10.1038/s41591-020-0916-2>.
6. Vaira Luigi Angelo, Hopkins Claire, Salzano Giovanni, Petrocelli Marzia, Melis Andrea, Cucurullo Marco, Ferrari Mario, Gagliardini Laura, Pipolo Carlotta, Deiana Giovanna, Fiore Vito, De Vito Andrea, Turra Nicola, Canu Sara, Maglio Angeloantonio, Serra Antonello, Bussu Francesco, Madeddu Giordano, Babudieri Sergio, Giuseppe Fois Alessandro, Pirina Pietro, Salzano Francesco A., De Riu Pierluigi, Biglioli Federico, De Riu Giacomo. Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter-study. *Head & Neck.* 2020; <https://doi.org/10.1002/hed.26269>.