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RESPONSE TO LETTER

# Ocular Symptoms in Long COVID: A Cross-Sectional Study [Response to Letter]

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## Dear editor

We thank Deng and Wang for their interest in our work and for their thoughtful and constructive comments. We are largely aligned with many of the points raised, which highlight important opportunities to refine future research on ocular symptoms in long COVID.

The concern regarding the use of a composite ocular symptom endpoint is well taken. Grouping symptoms such as blurred or decreased vision, dry eye, and floaters or flashes may obscure distinct underlying pathophysiological mechanisms and represents an important limitation of the current study. Future work would benefit from evaluating these symptom domains separately and incorporating objective ophthalmic assessments, including slit-lamp examination, tear film testing, ocular surface staining, optical coherence tomography, and optical coherence tomography angiography, to better distinguish ocular surface, autonomic, inflammatory, and retinal microvascular phenotypes.[1–3] At the same time, our study was designed as an epidemiologic, patient-reported symptom-burden analysis rather than a mechanistic ophthalmic phenotyping study.[4] Because the study was conducted during, or shortly after, the peak of the pandemic, when access to in-person clinical evaluation was limited, self-reported data represented the most feasible and inclusive approach. Restricting analyses only to participants who underwent clinical evaluation could have introduced selection bias. The LISTEN study was therefore intentionally designed to capture a broad spectrum of patient-reported symptoms across neurologic, cardiovascular, dermatologic, visual, and systemic domains, reflecting the heterogeneous nature of long COVID.[4] While this approach enabled comprehensive characterization of patient experiences, it necessarily came with trade-offs in granularity.

The point regarding potential confounding by increased screen time during the pandemic is also important. Data on screen exposure and pre-existing ocular conditions were not captured in the present cohort, which limits our ability to account for these factors. Prior studies have shown that increased screen exposure during the pandemic was associated with dry eye symptoms and digital eyestrain.[5,6] With the growing availability of device-based screen-time tracking, future studies may be well positioned to integrate such measures alongside environmental, behavioral, and baseline ocular health data to strengthen causal interpretation.

The predominance of female participants in the study is another important consideration, particularly given known sex- and gender-related differences in dry eye disease and the higher proportion of women reported in postural orthostatic tachycardia syndrome (POTS) cohorts.[7,8] In response to this concern, we conducted additional post hoc analyses stratified by participant-reported gender using the same composite ocular symptom outcome and the same Bonferroni correction approach from our original study.[4] Among female participants, new-onset POTS/dysautonomia remained more common among those with ocular symptoms (102/265, 38.5%) than those without ocular symptoms (28/172, 16.3%; $p < 0.001$). Among male participants, the same pattern was observed for new-onset POTS/dysautonomia (25/73 [34.2%] vs 7/77 [9.1%]; $p = 0.006$). Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) was numerically more common among participants with ocular symptoms in both female and male strata, but these comparisons were not statistically significant

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(female: 53/265 [20.0%] vs 16/172 [9.3%], p = 0.093; male: 15/73 [20.5%] vs 6/77 [7.8%], p = 0.830). These exploratory analyses suggest that the association between ocular symptoms and POTS/dysautonomia was not explained solely by the female predominance of the cohort, while the gender-stratified ME/CFS findings should be interpreted more cautiously.

It is also likely that the ocular symptoms observed in long COVID reflect heterogeneous underlying mechanisms, including autonomic dysfunction, ocular surface inflammation, and retinal microvascular changes.[2–4] However, the cross-sectional design limits our ability to assess temporal relationships or establish causality and therefore precludes definitive mechanistic conclusions. We agree that future longitudinal studies incorporating objective ophthalmic testing, autonomic phenotyping, and baseline ocular history will be necessary to clarify these relationships.

Finally, we agree that integrating ocular symptom screening into long COVID care pathways may be valuable, particularly when symptoms affect quality of life or daily functioning. Validated instruments such as the Ocular Surface Disease Index may help standardize symptom assessment, while multidisciplinary collaboration between ophthalmology, primary care, neurology, and other specialties may improve recognition and management of patients with overlapping ocular and systemic symptoms.[3,9] Implementation, however, will likely depend on local resources, healthcare infrastructure, and the availability of referral pathways.

We again thank Deng and Wang for their thoughtful commentary. Their letter underscores the need for longitudinal studies that combine patient-reported outcomes, objective ophthalmic examination, autonomic assessment, screen-time exposure data, and more diverse participant recruitment. Our study provides an epidemiologic foundation for recognizing ocular symptoms within the broader long COVID symptom burden, while future work should clarify mechanisms, temporality, and targeted management strategies.

## Data Sharing Statement

The data used in this study is not publicly available due to participant privacy but is accessible in a deidentified format upon reasonable request from the corresponding author, HMK.

## Ethics Approval and Consent to Participate

The Yale University Institutional Review Board granted approval for the LISTEN study on April 1, 2022. Participants consented to the study through electronic forms. The conduct of LISTEN adheres to the principles outlined in the Declaration of Helsinki and follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for observational studies.

## Consent for Publication

All authors have read and approved the final manuscript and consent to its publication.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

Harlan M Krumholz received expenses and/or personal fees from Element Science, Identifeye, and F-Prime in the past three years. He is a co-founder of Refactor Health and Ensight-AI. He and his spouse are co-founders of, and have equity

in, Hugo Health, the personalized health data platform company that developed the Hugo Kindred platform. His spouse is an officer with Hugo Health. The Yale Conflict of Interest Committee oversees his involvement in this study. He was the editor *of Journal Watch: Cardiology of the Massachusetts Medical Society* and is a section editor for *UpToDate*. He is associated with contracts, through Yale New Haven Hospital, from the Centers for Medicare & Medicaid Services, and through Yale University from Janssen, Johnson & Johnson Consumer, and Pfizer. The other authors have no conflicts of interest to disclose for this communication.

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