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Response to Letter to Editor

Response to Comment on "*ApoE* e4e4 Genotype and Mortality With COVID-19 in UK Biobank" by Kuo et al.

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Nikogosov et al. questions 2 main issues related to our *APOE* and COVID-19 letters (1,2). These focus on the initial candidate gene analysis reporting an association which was not genome-wide significant, with the suggestion that this somehow undermines genome-wide association studies (GWAS). Secondly, our choice of control group is questioned.

On the first issue, our work was undertaken after the COVID-19 Host Genetics Initiative (https://www.covid19hg.org/) was set up to enable pooled GWAS analyses of COVID-19 host genetics. Given that dementia had emerged as a major risk factor for severe COVID-19 (3), we hypothesized that the dementia risk haplotype *APOE* e4 could be an important factor. Genome-wide association studies are designed to test single base variant associations, usually employing additive models. Additional analyses are therefore needed to analyze complex haplotypes like those of *APOE*, combining 2 separate variants and requiring genotype-based analyses with no presumption of the inheritance mode, which are not part of the standard GWAS analysis. We therefore undertook this additional analysis, with no risk of undermining the GWAS effort for COVID-19.

The authors point out that the *APOE* e4e4 association we reported reached genome-wide significance ($p < 5 \times 10^{-8}$) in our second analysis after additional data became available, but not in the first. We agree that under normal circumstances, it would not have been ideal to publish non-genome-wide significant results, at least without strong a priori evidence. However, at the time of writing, data on COVID-19 host genetics were extremely scarce, and given the global health emergency created by the pandemic, and the importance of dementia as a risk factor for severe COVID-19, we believe our work was a useful contribution, with early publication inviting others to examine this potential risk mechanism.

The second issue raised by Nikogosov et al. relates to the UK Biobank providing data on whether the patients tested for COVID-19 were hospital inpatients, and suggesting that the valid comparison should have been between inpatient positives and positives not admitted to hospital. However, the data available at the time were actually derived from the test samples sent to laboratories, stating only where the patient was when the test sample was taken (4). Thus, patients may have been recorded as being in a non-inpatient setting when tested but could have been admitted to hospital soon after. Therefore, the suggested design from Nikogosov et al. would not have been measuring what they suggest, likely biasing the association to the null (5). We note that the only published GWAS to date compared cases with respiratory failure to convenient controls regardless of COVID-19 test results, including blood donors randomly selected for the study and genotyped controls from previous studies (6). Our comparison with the rest of the UK Biobank participants (negative/unknown), therefore, provided a less-selected control group without evidence of COVID-19 and had better statistical power compared to the outcome of inpatient positives versus non-inpatient positives.

Conflict of Interest

References

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