Does antipsychotic use mediate the effect of psychiatric disorders on COVID-19?

Authors' reply

We thank Augusto Ferraris and colleagues for their important comments on our study.[1] We share their interest in advancing understanding on the potential mechanisms that underlie our observed associations. One possibility is the potential role of psychotropic drugs, such as antipsychotic medications, as suggested by Ferraris and colleagues.

The UK Biobank has data on the use of antipsychotic medications from the baseline questionnaire and from linked primary care prescription data. Inspired by Ferraris and colleagues' hypothesis, we tested whether use of antipsychotic medications could mediate our reported associations by restricting the analysis to 415 381 individuals with no history of antipsychotic use (98·7% of the original study population). The results from this additional analysis were largely similar to our original results. The fully adjusted odds ratios were 1·49 (95% CI 1·32–1·68), 1·59 (1·38–1·83), and 2·04 (1·59–2·63) for all COVID-19 cases, inpatient COVID-19 cases, and COVID-19-related deaths, respectively, comparing individuals with psychiatric disorders to those without such disorders. Although not a full mediation analysis, these new results suggest little, if any, influence of antipsychotic use on the observed associations.

Indeed, previous studies on antipsychotic use and the risk of infection, as cited by Ferraris and colleagues, are observational and, as a result, might suffer from indication bias. In other words, it is possible that the use of antipsychotic medications is more an indicator of the severity of psychiatric disorders, and that the heightened risk of infections among antipsychotic users reflects other biological sequelae of severe psychiatric conditions rather than the medications themselves.[2] However, other psychotropic medications might also have a role in the associations between psychiatric disorders and susceptibility to various infections, and should be the subject of further studies. For example, in our previous studies on the association between stress-related disorder and risk of life threatening infections[3] and autoimmune disease,[4] we showed a decreased relative risk of immune-related outcomes among patients with stress-related disorder who received long-term treatment with selective serotonin reuptake inhibitors. Similarly, a protective role of benzodiazepines on community-acquired pneumonia has also been reported.[5]

In conclusion, although we were not able to confirm Ferraris and colleagues' hypothesis, we agree with them that further research is needed to understand the underlying mechanisms that link pre-existing psychiatric disorders and susceptibility to infections, including COVID-19, focusing on potential genetic, environmental (including use of psychotropic drugs), and epigenetic factors.

We declare no competing interests.

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For more on the **UK Biobank data** see https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=Data_providers_and_dates