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## Disentangling the complex bidirectional associations between COVID-19 and psychiatric disorder

In *The Lancet Psychiatry*, Maxime Taquet and colleagues<sup>1</sup> reported that survivors of COVID-19 appear to be at increased risk of psychiatric sequelae, and that a psychiatric diagnosis might be an independent risk factor for COVID-19. We are concerned that several limitations might weaken the bidirectional associations between COVID-19 and psychiatric disorder.

First, evidence suggests that the medical isolation of hospitalised patients might have a negative effect on their mental wellbeing and behaviour, with higher levels of depression and anxiety among isolated patients.<sup>2</sup> Therefore, the psychiatric sequelae of COVID-19 might result from isolation for COVID-19. Future studies are warranted to examine the incidence of psychiatric diagnoses in individuals who tested negative for severe acute respiratory syndrome coronavirus 2 infection but were subject to the same quarantine period as those who tested positive. Second, the pharmacotherapy for the management of COVID-19 might induce psychiatric adverse effects. For example, corticosteroid-induced psychiatric adverse effects are common and include depression, insomnia, anxiety, and cognitive deficits.<sup>3</sup>

Finally, this study did not control for the use of psychotropic drugs in the analysis. A recent randomised clinical trial<sup>4</sup> reported that fluvoxamine was associated with a reduction in clinical deterioration in patients with COVID-19, and that the mechanism might be related to the sigma-1 receptor-associated immune modulation. In addition to fluvoxamine, fluoxetine and escitalopram also have high potency at the sigma-1 receptor.<sup>5</sup> Vulnerability

to COVID-19 might be modulated by the use of these antidepressant drugs. In conclusion, we believe that further research to minimise bias and confounding might help disentangle the complex bidirectional associations between COVID-19 and psychiatric disorder.

We declare no competing interests.

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- 1 Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry* 2020; published online Nov 9. [https://doi.org/10.1016/S2215-0366\(20\)30462-4](https://doi.org/10.1016/S2215-0366(20)30462-4).
- 2 Abad C, Fearday A, Safdar N. Adverse effects of isolation in hospitalised patients: a systematic review. *J Hosp Infect* 2010; **76**: 97–102.
- 3 Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc* 2006; **81**: 1361–67.
- 4 Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA* 2020; **324**: 2292–300.
- 5 Ishima T, Fujita Y, Hashimoto K. Interaction of new antidepressants with sigma-1 receptor chaperones and their potentiation of neurite outgrowth in PC12 cells. *Eur J Pharmacol* 2014; **727**: 167–73.

### Authors' reply

We thank Yi-Fan Lo and colleagues for their comments about our Article.<sup>1</sup> We agree that minimising confounding and bias is important, which is why we used extensive propensity score matching and a range of comparison cohorts and sensitivity analyses. We noted in our Article that there are various explanations for the observed associations between COVID-19 and psychiatric outcomes, and the issues raised by Lo and colleagues— isolation and medication—are examples of possible mediators. Isolation and other psychosocial factors are difficult to measure, let alone control for, but we can offer some clarification regarding

the medications mentioned. In our study population, corticosteroids were prescribed less commonly in the 2 weeks after a diagnosis of COVID-19 than after other respiratory infections (12.6% vs 19.8%). Moreover, as noted in the appendix of the Article, associations between COVID-19 and psychiatric disorders were seen in patients who were not admitted to hospital and who were thus very unlikely to have been prescribed corticosteroids. These results do not support corticosteroids being a major influence on the results. Lo and colleagues also mention fluvoxamine, but this drug was prescribed to only 0.03% of patients with COVID-19; the possible effect of more commonly used antidepressants on outcomes requires further investigation.

The declaration of interests remains the same as in the original Article.

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- 1 Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry* 2020; published online Nov 9. [https://doi.org/10.1016/S2215-0366\(20\)30462-4](https://doi.org/10.1016/S2215-0366(20)30462-4).

### Exposure to patient suicide and early career psychiatrists

The editors of *Lancet Psychiatry* recently emphasised the negative effects of patient suicide on psychiatrists.<sup>1</sup> Their editorial describes how patient suicide can profoundly affect psychiatrists in both their personal and professional lives through complex emotional turmoil.

However, the editors insufficiently highlight the fact that first exposure to patient suicide happens more often during residency and early career and that this early exposure is highly