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Psychiatric disorders and risk of infections: early lessons from COVID-19

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In *The Lancet Healthy Longevity*, Huazhen Yang and colleagues[1] used community-based longitudinal data from 421 014 UK Biobank participants to assess the risk of COVID-19 morbidity and mortality among middle-aged and older adults (mean age 67·80 years) with pre-pandemic clinical diagnoses of psychiatric disorders. The authors used logistic regression to estimate odds ratios (ORs) for the associations between pre-pandemic hospitalisation for a psychiatric disorder and three separate COVID-19-related outcomes: any diagnosis of COVID-19 (regardless of severity), inpatient hospitalisation for COVID-19, and COVID-19-related death. The authors also estimated ORs for hospitalisation for other infections, unrelated to COVID-19.

Yang and colleagues showed that pre-pandemic psychiatric hospitalisation was associated with elevated odds of any COVID-19 diagnosis (OR 1·44, 95% CI 1·28–1·62), COVID-19 inpatient hospitalisation (1·55, 1·34–1·78), and COVID-19-related death (2·03, 1·59–2·59). This association was greater for individuals with hospitalisation for more than one psychiatric disorder. People with pre-pandemic psychiatric hospitalisation also had an elevated risk of hospitalisation for other infections, possibly suggesting shared underlying mechanisms. These findings provide crucial information for understanding who is at greatest risk for COVID-19, and also add to a growing body of evidence suggesting that mental and somatic health are closely intertwined.

Research has shown that psychological stress,[2] as well as specific psychiatric disorders (eg, post-traumatic stress disorder,[3,4] depression,[5] and adjustment disorder[4,6]), are associated with increased incidence of various infections (eg, respiratory infections, sepsis, and herpes zoster). As Yang and colleagues note, potential mechanisms explaining these associations involve immune dysregulation processes such as proinflammatory cytokine production and heightened hypothalamic-pituitary-adrenal axis activity.[7] Changes to health behaviours in response to stress (eg, altered diet and exercise patterns) are also possible explanations for the observed associations.[8] A crucial next step in this area of research will be to determine whether the association between psychiatric disorders and infections is indeed causal, and to assess the relative contributions of potential mechanisms of these associations.

Yang and colleagues' study contributes to the existing literature on psychiatric disorders and infections in important ways. First, concerns about reverse causation are minimised. A valid critique of studies on psychiatric disorders and infections is that infections might be present before the onset of psychiatric disorders and might be undetected or underreported (eg, when infections commonly recur or resolve without treatment). Additionally, studies have suggested that infections are also risk factors for psychiatric disorders.[9] For these reasons, it is challenging to elucidate the direction of the association between psychiatric disorders and infections. By examining outcomes related to a novel infection that did not exist when participants were diagnosed with psychiatric disorders, this study explicitly supports the notion that psychiatric disorders could increase susceptibility to infections.

Second, this study goes beyond the existing literature by formally addressing surveillance bias, which would be expected if individuals with psychiatric disorders were more likely to be tested for the virus that causes COVID-19 because of established contact and increased interaction with the health-care system. Yang and colleagues did a quantitative bias analysis that showed that, for each COVID-19 outcome, cases among people without pre-pandemic psychiatric hospitalisation would need to have been underestimated by more than 50% to nullify the observed associations. Surveillance bias and other forms of differential misclassification bias can greatly affect results. Using assumptions about the extent of case under-ascertainment to quantify the expected effect of surveillance bias adds great value to this study.

While aiding in our general understanding of psychiatric disorders and infections, the findings of this study can also be acted upon during the COVID-19 crisis. Some demographic groups, such as older adults and people with specified somatic conditions (eg, heart disease, diabetes, and asthma), have been identified

as high-risk for COVID-19. The evidence presented by Yang and colleagues suggests individuals with existing psychiatric disorders might be another high-risk group. These results not only reveal an important subpopulation for targeted prevention efforts, but are also especially important given the effect of the COVID-19 pandemic on mental health.[10] It is becoming increasingly apparent that COVID-19 has worsened mental health for many people, even those who were mentally healthy before the pandemic,[11] and that the prevalence of mental illness will likely increase.[10] This increase might, in turn, increase vulnerability to COVID-19 and other infections. Additional studies are needed to better understand the association between the severity of psychiatric disorders and the increased risk of infection susceptibility.

Future work should assess the generalisability of Yang and colleagues' findings. First, it is important to understand the effects of psychiatric disorders that do not require hospitalisation on susceptibility to infections such as COVID-19. Yang and colleagues took a first step towards filling this gap by doing a sub-analysis of participants with available primary care data. They found that people diagnosed with a psychiatric disorder only in a primary care setting had increased odds of COVID-19 outcomes, albeit to a lesser extent than people hospitalised for psychiatric disorders (OR 1·43, 95% CI 1·22–1·68 for any COVID-19 diagnosis; 1·44, 1·18–1·76 for COVID-19 inpatient hospitalisation; and 1·53, 1·05–2·22 for COVID-19-related death). Second, future work should assess whether younger people with psychiatric disorders are also at increased risk of COVID-19 morbidity and mortality. Third, similar analyses should be done in more diverse community samples, as 95% of participants in Yang and colleagues' study were white, and COVID-19 is disproportionately impacting racial and ethnic minority groups.[12]

This work on COVID-19 is just one example of a dynamic and growing area of research into the link between psychiatric disorders and infections. By addressing some common methodological concerns specific to this topic, Yang and colleagues' study advances the fields of psychiatry, immunology, and epidemiology in general, while also offering findings that inform specific responses to the COVID-19 pandemic.

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