Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

The DOSMD challenge and the COVID-19 conundrum

Dear Editor,

The recent article published in your journal on schizophrenia research during the novel coronavirus disease (COVID-19) pandemic (Cowan, 2020) not only made a convincing and commendable case for continuing such research, but discussed the possibility of a biological link between human coronavirus infections and schizophrenia. In this connection, I wish to make some relevant supplementary observations.

The World Health Organization's international studies of schizophrenia – the International Pilot Study of Schizophrenia (IPSS) and the Determinants of Outcome of Severe Mental Disorders (DOSMeD) both found that the outcome of schizophrenia was significantly better in developing countries, particularly in terms of remission rates and periods of unimpaired functioning (Jablensky et al., 1992). Though these findings have been criticized on the basis of divergent results from low- and middle-income countries (Cohen et al., 2008), significant evidence remains for differential outcomes in developed and developing countries even when the follow-up period is extended (Jablensky and Sartorius, 2008). Possible explanations for this finding are likely to be complex, and may include genetic variation, cultural factors, gene-environment interactions and even methodological concerns; however, none of these has been conclusively proved (Edgerton and Cohen, 1994; Jablensky and Sartorius, 2008). Finding an explanation for this difference in outcomes, sometimes referred to as the "DOSMD challenge" (Edgerton and Cohen, 1994), remains an important unsolved problem in psychiatry.

Today, in the face of the COVID-19 pandemic, a similar paradoxical finding has emerged: patient outcomes, particularly in terms of case fatality, appear to be more favourable in some developing countries (Al-Tawfiq et al., 2020). Some of this variation may be more apparent than real, due to variations in the availability of testing facilities or personnel for contact tracing, or the presence of infected but asymptomatic individuals (Rajgor et al., 2020). However, even if these factors are taken into account, significant variability still exists, with higher fatality rates noted in certain developed countries (Khafaie and Rahim, 2020). Though social customs and political factors have been proposed as an explanation for variations in prevalence, they cannot explain the wide variability in mortality (Al-Tawfiq et al., 2020).

The link between these two puzzling questions may be closer than is immediately apparent. Historically, infectious disease burden has been an important driver of human culture-gene co-evolution. Higher pathogen prevalence exerts an evolutionary pressure that favours more collectivistic cultural practices (Fincher et al., 2008), at least some of which may be mediated through specific genetic polymorphisms (Chiao and Blizinsky, 2010; Way and Lieberman, 2010). Such practices, which are more commonly seen in developing countries, may have a positive influence on outcome in schizophrenia (Weisman, 1997) as well as in minimizing the spread of infectious disease (Fincher et al., 2008; Al-Tawfiq et al., 2020).

More relevantly for the question at hand, pathogen prevalence has also been associated with population-level variations in genes regulating immune function, such as the interleukin-6 (IL-6) gene, and these variations have also been correlated with indices of cognition and economic development (Napolioni and MacMurray, 2016). IL-6 has been associated with a variety of negative outcomes in schizophrenia, including more severe positive and negative symptoms, greater cognitive impairment, and a poorer response to treatment (Momtazmanesh et al., 2019). IL-6 and its receptor also play a key role in the inflammatory cascade, sometimes referred to as a "cytokine storm", that has been associated with more severe lung disease as well as multiple organ dysfunction and death in patients with COVID-19 (Hirano and Murakami, 2020). This provides at least a preliminary and plausible explanation of how genetic variations in immune function, driven by pathogen pressure in different countries, could influence adverse outcomes both in schizophrenia and in COVID-19. Similar mechanisms could be involved in the link between coronavirus infection and schizophrenia itself. One candidate that could be investigated in this context is the rs1800795 (−174 G/C) polymorphism of the *IL6* gene. The *G* allele of this variant, more frequent in developing countries, is associated with an enhanced host immune response to pathogens (Napolioni and MacMurray, 2016), while the *C* allele, which is somewhat more frequent in developed countries, has been associated with celiac disease – an autoimmune disorder linked to schizophrenia (Dema et al., 2009; Kalaydjian et al., 2006). Similarly, the association between population frequencies of genetic variants that have been associated with social sensitivity and therefore with collectivist social norms – such as the serotonin transporter polymorphism 5-HTTLPR, the mu opioid receptor polymorphism OPRM1 A118G, and the MAOA-uVNTR variant of the monoamine oxidase A gene (Way and Lieberman, 2010) and the outcome of schizophrenia across nations and cultures could be examined. The latter approach would test the hypothesis of genetic variants positively influencing the outcome of schizophrenia via their effects on social and cultural practices which evolved primarily as a defence against infection.

In conclusion – and returning to the question posed by Cowan in his paper – not only is schizophrenia research relevant during the COVID-19 pandemic, but studying the complex links between pathogen prevalence, population genetics, culture and immune function may shed light not only on schizophrenia but on a variety of immune-related outcomes and diseases (Stringer et al., 2014), including some that may be of direct relevance to COVID-19 itself. The DOSMD challenge and the COVID-19 conundrum may, in fact, share at least some common biological explanations.

Contributors

Dr. Ravi Philip Rajkumar developed the concept of this study, extracted the data from the relevant sources, analyzed it and wrote the manuscript.

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Declaration of competing interest

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