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Identifying causal role of COVID-19 in immunopsychiatry models

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1. Scenario 1: Control for COVID-19 when it is a confounder

There are several immunopsychiatry examples in which COVID-19 may be appropriately considered a confounder, including research on inflammation and mortality risk. We simulated scenarios in which the virus directly elicits a host immunological response (i.e., inflammation) with either a weak (β = 0.10) or strong (β = 0.50) effect and also directly impacts mortality, again with both weak and strong effects. In all four scenarios, the direct relationship between inflammation and mortality was set to β = 0.30. As shown in Fig. 1, models that test the direct relationship with COVID-19 as a covariate are unbiased, but models that omit the virus are positively biased. Furthermore, bias was unmitigated by sample size. In the case when COVID-19 causes both the outcome and predictors of interest in a study, it must be treated as a confounder and statistically controlled, or estimates will be biased.

2. Scenario 2: Do not control for COVID-19 when it is a mediator

Other immunopsychiatric-related research questions exist in which COVID-19 may be conceptualized as mediating key pathways among other variables. For example, we simulated scenarios in which the indirect effect of COVID-19 as a mediator is considered. As shown in Fig. 2, models that omit the virus best estimate the total effect of SES on distress (i.e., the total effect). Unless researchers are interested in the effect of all pathways from SES to respiratory distress except COVID-19, they should not include the virus as a covariate in their models, or their estimates will not capture the full...
Fig. 1. Values are simulated from this causal model using the lavaan (Rosseel, 2012) package, with varying sample sizes; each combination of population parameters and sample size was simulated 10,000 times. The causal relationship of inflammation to mortality is set to 0.30. This association was tested using both a simple linear model and a regression model with COVID-19 as a covariate. Estimates of the parameter are depicted using boxplots; a solid, horizontal line represents the true population parameter, for reference. Code to recreate these simulations can be found at https://github.com/sjweston/PNI-covid-simulation.

Fig. 2. Data were simulated from models in which COVID-19 mediates the causal relationship between socioeconomic status (SES) and respiratory distress. Values are simulated from this causal model using the lavaan (Rosseel, 2012) package, with varying sample sizes; each combination of population parameters and sample size was simulated 10,000 times. The direct causal relationship of SES to inflammation is set to 0.30. The association between SES and inflammation was tested using both a simple linear model and a regression model with COVID-19 as a covariate. Estimates of the parameter are depicted using boxplots, which horizontal lines at the true direct effect – in all simulations – and also at the true indirect effect (calculated by multiplying the true causal pathways to and from COVID-19) and the true total effect (calculated by adding the direct and indirect effects), for reference. Code to recreate these simulations can be found at https://github.com/sjweston/PNI-covid-simulation.
pathway (see Fig. 3). Again, larger samples do not mitigate the amount of bias.

3. Scenario 3: Ambiguity about COVID-19 as confounder versus mediator

A significant challenge is how to address research where a strong argument could be made to support COVID-19 as either a confounder or mediator. An example is research on the causal impact of immune functioning on depression, in which it is unclear where to incorporate COVID-19 in the model. It can be argued that those with low immune functioning are more susceptible to contracting the virus; yet, there is no doubt that those who contract COVID-19 suffer short-term declines in immune functioning as they recover. In this case, it is difficult to strictly dictate methodological choices, as doing so requires knowing the true underlying model. Establishing temporal precedence can help guide decisions. Overall, we recommend that in these circumstances, researchers should present both zero-order and partial relationship.

4. Future directions

In summary, the challenge for immunopsychiatry researchers is to identify the causal effects of COVID-19 and appropriately incorporate these effects into theoretical causal models. The COVID-19 pandemic is an unprecedented test for the field; yet, immunopsychiatry is also uniquely poised to meet this challenge and rigorously examine the impact of the virus on the human body and mind for years to come.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.05.066.

References

Ahmed, F., Ahmed, N.E., Pissarides, C., Stiglitz, J., 2020. Why inequality could spread COVID-19. Lancet Public Health.

COVID, C., 2020. Response team. Geographic differences in COVID-19 cases, deaths, and incidence—United States, February 12-April 7, 2020. MMWR Morb. Mortal Wkly. Rep. 69 (15), 465–471.

Furukawa, N.W., Brooks, J.T., Sobel, J., 2020. Evidence supporting transmission of severe acute respiratory syndrome coronavirus 2 while presymptomatic or asymptomatic. Emerg. Infect. Diseases.

Holmes, E.A., O’Connor, R.C., Perry, V.H., Tracey, I., Wessely, S., Arseneault, L., Ford, T., 2020. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. Lancet Psychiatry.

Kroencke, L., Geukes, K., Utesch, T., Kuper, N., Back, M. (2020). Neuroticism and Emotional Risk During the Covid-19 Pandemic.

Rosseel, Y., 2012. Lavaan: An R package for structural equation modeling and more. Version 0.5–12 (BETA). Journal of Statistical Software 48 (2), 1–36.

Troyer, E.A., Kohn, J.N., Hong, S., 2020. Are we facing a crushing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav. Immun.

Wang, C., Pan, R., Wan, X., Tan, Y., Xu, L., Ho, C.S., Ho, R.C., 2020. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int. J. Environ. Res. Public Health 17 (5), 1729.

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Tai, Y., 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir. Med. 8 (4), 420–422.

Yancy, C.W., 2020. COVID-19 and African Americans. JAMA.