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.

Brain, Behavior, and Immunity 88 (2020) 6–8

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Identifying causal role of COVID-19 in immunopsychiatry models

Sarah R. Horn[a,b,*], Sara J. Weston[a,b], Philip A. Fisher[a,b]

[a] Department of Psychology, University of Oregon, Eugene, OR, United States
[b] Center for Translational NeuroScience, University of Oregon, Eugene, OR, United States

The coronavirus disease 2019 (COVID-19) pandemic has rapidly evolved into one of the most serious public health crises in recent history. As COVID-19 continues to spread globally, the field of immunopsychiatry is correspondingly adjusting our studies while maintaining high-quality research standards (Holmes et al., 2020). This goal necessitates significant flexibility given the gaps in our knowledge base and the quickly developing shifts in available information. The primary obstacle in many parts of the world is the inability to precisely discern the proportion of our samples that have been or are currently infected with COVID-19, a problem compounded by the high rates of asymptomatic or pre-symptomatic presentations (Furukawa et al., 2020). Currently, without widespread testing, the field must creatively adopt strategies to properly assess and then account for COVID-19.

Several factors have been shown to increase the likelihood of contracting the virus or developing a more severe presentation of the illness. In the absence of direct assessment of COVID-19, proxy variables represent a resourceful way to consider the role of the virus in germane immunopsychiatric research. Examples include personality traits (e.g., neuroticism; Kroencke et al., 2020), geographic location (CDC, 2020), occupation, working from home versus community, socioeconomic status (SES) (Ahmed et al., 2020), racial/ethnic and minority status (Yancy, 2020), underlying health conditions (CDC, 2020), mental health symptomatology (Wang et al., 2020), and proximity to documented cases. As access to testing improves, there may be unique strategies to more accurately estimate the rates of exposure in specific locations (e.g., comparing to another location with a similar geographic or demographic background with a comparable infection rate). Expectedly, several of these factors align strongly with an immunopsychiatry framework, highlighting further the strong connections between stress, physical and mental health, and immunological processes that are particularly relevant in the wake of COVID-19.

Under these circumstances, causal models in immunopsychiatry will, for the foreseeable future, need to account for COVID-19. Furthermore, correctly specifying the role of COVID-19 in these models is critical for hypothesis testing. A central issue is whether COVID-19 is treated as a confounding variable (e.g., as causal influence on both inflammation and mental health symptoms; Wang et al., 2020) or a mediating variable. (e.g., explaining the causal link between hypercytokinemia and physical outcomes; Troyer et al., 2020). In this paper, we examine implications for conceptualizing and analyzing measures associated with COVID-19 (e.g., diagnosis, viral load) as confounding versus mediating variables. To explore the implications of this distinction, we visualize simulated data varied according to sample and effect size, as well as the role of COVID-19 in the causal model. We consider the statistical implications of each of these scenarios.

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 ($\beta = 0.10$) or strong ($\beta = 0.50$) 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 $\beta = 0.30$. 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 low SES is a cause of COVID-19 (e.g., through pathways such as increased financial pressure to work; Ahmed et al., 2020), and COVID-19 in turn causes respiratory distress (Xu et al., 2020). Like before, we simulated effect sizes leading to and away from COVID-19 as either strong or weak, and set the direct relationship between the predictor and outcome of interest (SES and respiratory distress, respectively) to a moderate effect size. 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

* Corresponding author.

https://doi.org/10.1016/j.bbi.2020.05.066
Received 22 May 2020; Accepted 24 May 2020
Available online 29 May 2020

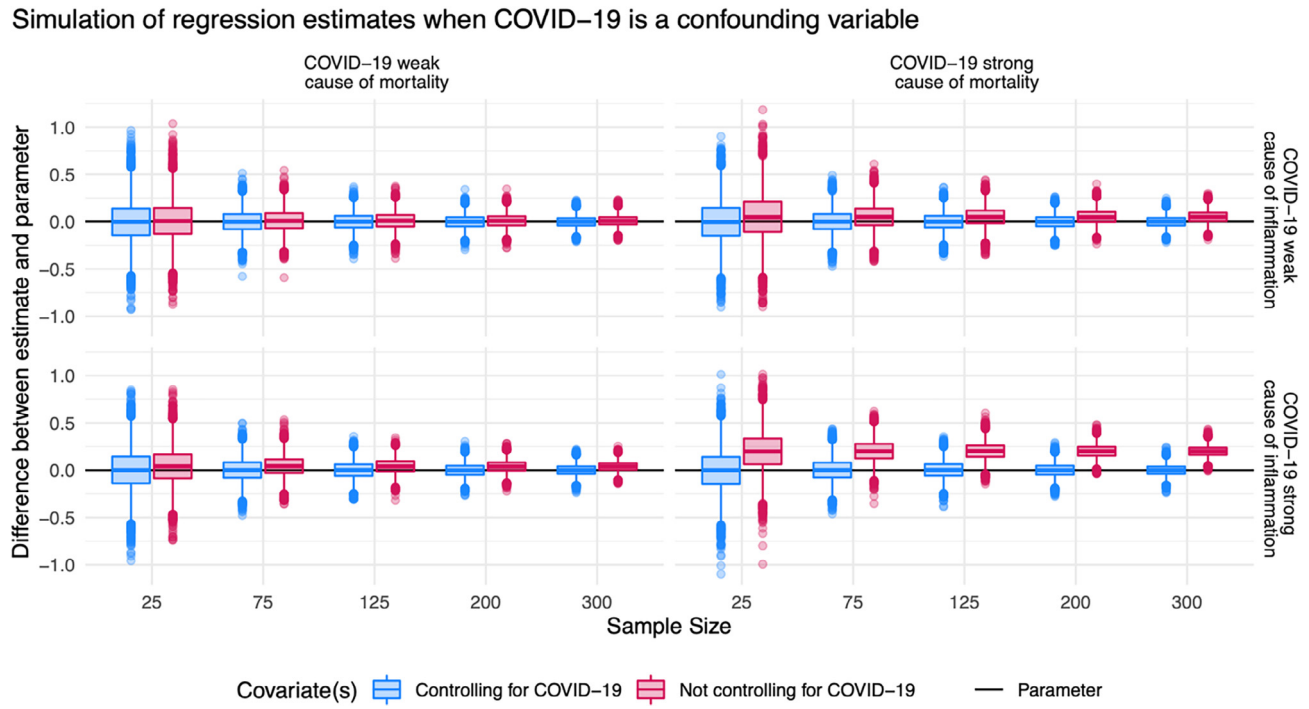

Fig. 1. Values are simulated from this causal model using the *lavaan* (Rosseel, 2012) package, with varying sample sizes; each combination of population parameters and sample size was simulated 10,000 times. The causal relationship of inflammation to mortality is set to 0.30. This association was tested 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.

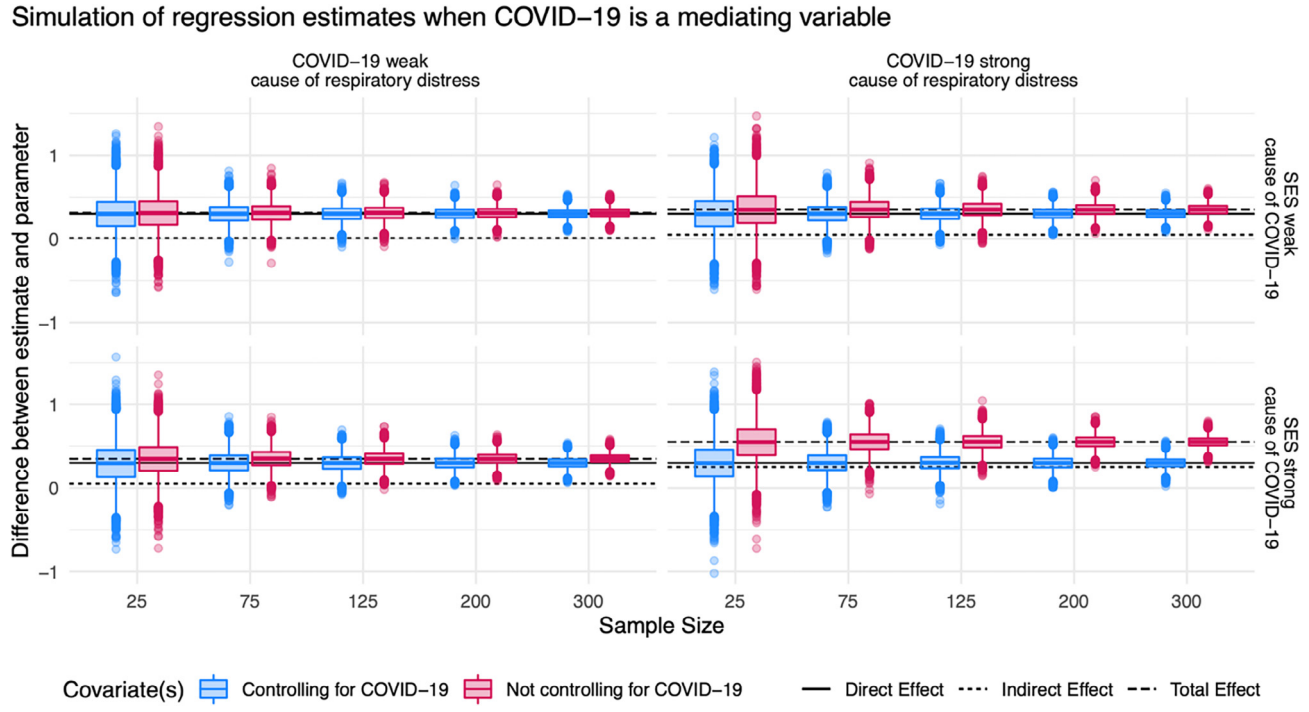

Fig. 2. Data were simulated from models in which COVID-19 mediates the causal relationship between socioeconomic status (SES) and respiratory distress. Values are simulated from this causal model using the *lavaan* (Rosseel, 2012) package, with varying sample sizes; each combination of population parameters 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.

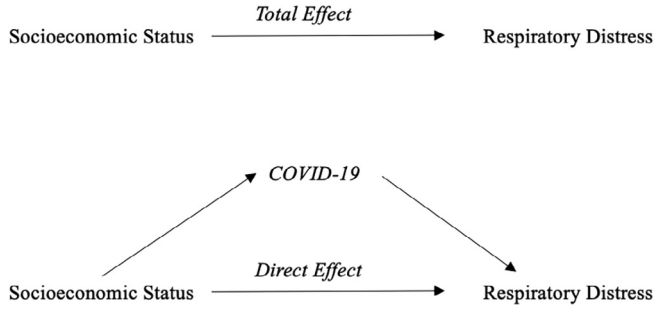

Fig. 3. Example Mediation Model.

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 crashing 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.