Review of: "Cross-national associations of IQ and infectious diseases: Is the prevalence of Corona an exceptional case?"

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Potential competing interests: No potential competing interests to declare.

This paper presents the results of a cross-national analysis examining the relationship between estimated national IQ and indices of the severity of the COVID-19 pandemic.

Although cross-national ecological studies rank relatively “low” in the hierarchy of epidemiological evidence, they are useful for generating leads that can be tested in more rigorous designs, and for identifying associations that may be difficult to observe at an individual level. Given the public health importance of identifying factors that are linked to pandemic vulnerability or resilience, there is a clear rationale for research of this kind.

The authors have used national IQ estimates from a compilation of various sources. Though there are significant controversies about the reliability and validity of national IQ estimates, they represent the “best available” measure of average cognitive capacity at a national level; therefore, I do not consider this a significant limitation for this sort of preliminary research. (Moreover, the data obtained in this study could be used to test the hypothesis more rigorously - e.g., within a country, do patients' individual IQs predict their likelihood of COVID-19 infection, complications or mortality)? It would, however, be interesting to conduct a sub-group analysis in those countries where there is unlikely to be a controversy about the validity of national IQ (i.e., in those where there is recent, good-quality data, and excluding those countries with a mean value of <70 or <60).

Regarding COVID-19 indices, there are some issues with the use of prevalence and mortality rates - namely, they depend on population size to a large extent. (For example, Singapore, which has a very small population, had a high COVID-19 prevalence in the initial stages of the pandemic, though there were very few cases in absolute terms). One way of addressing this is to correct analyses for population / population density, or to use an alternative outcome measure such as the case-fatality ratio (number of deaths divided by number of cases). There are also issues related to variations in COVID-19 testing policy in various countries (for example, in a country with a high population and limited health and economic resources, testing of asymptomatic cases / contacts may not be done with much rigour, leading to underestimation of prevalence and over-estimation of mortality-related statistics).

The authors have controlled for a large number of confounding factors, which is commendable. However, there are other potential confounders (i.e., variables that could be linked to both IQ and COVID-19 outcomes) that would be worth considering for inclusion in the analyses:

1. Measures of cultural individualism / collectivism (e.g., Hofstede's index or the Global Collectivism Index) - high national

IQ correlates positively with national individualism, and individualism (rather than IQ) may be linked to non-adherence to preventive or confinement measures.

2. Measures of “lifestyle diseases” / risk factors such as obesity, diabetes mellitus, cardiovascular disease - these are associated with worse outcomes after COVID-19 infection, and some of them are more common in high-income countries.
3. Vectors of spread such as air travel - in a study of COVID-19 statistics in India, case loads were higher in states with an international airport (which could lead to more rapid spread of cases across countries). Countries with high IQ / educational attainment / income may have higher levels of air travel, possibly leading to increased pathogen exposure and higher incidence rates.

When discussing the broader hypothesis of a link between IQ and infectious diseases, it might also be worth discussing the possibility of reverse causality, as mentioned in Napolioni and MacMurray (Brain Behav. Immun. 2016) in which high rates of infectious disease burden interact with genetic polymorphisms to cause altered brain development and neuroinflammation, leading to lower IQs. This may not be directly relevant to the COVID-19 pandemic but is worth considering as part of the “bigger picture".

Overall, I found this paper to be well-written, and the statistical analyses were conducted with appropriate precision and rigour. The study's results are intriguing, and I would consider it acceptable for publication with minor revisions (as mentioned above).