5th May 2021

Professor Carmine Pariante, PhD

Editor-in-Chief: Brain, Behavior, and Immunity

Dear Professor Pariante,

***Original Article*: Pre-pandemic Cognitive Function and COVID-19 Vaccine Hesitancy: Prospective Cohort Study**

In recent correspondence, we discussed potential interest from *Brain, Behavior, and Immunity* in this manuscript.

It has recently received a favourable evaluation from JAMA Network Open; for instance, the referees remarked that our submission was a …”very great read and timely article” and that they ….”.. look forward to reading the final product.”. Moreover, all the critical points raised were helpful and can be readily addressed, either by straightforward sensitivity analyses or further commentary.

We were therefore surprised by the editorial decision to reject the manuscript.

You suggested that, if we addressed the various criticisms in detail, you would consider our manuscript for publication.

Below, we take each of the referees’ comments on a point-by-point basis. In the process, we have conducted a series of substantial subsidiary analyses.

We look forward to hearing from you.

Sincerely,



David Batty PhD, DSc

*Professor of Epidemiology, University College London*

*Honorary Professor, University of Edinburgh*

**Editor’s decision**

We discussed this at length and have lots of concerns, including the long period between cognitive testing and the survey.

**Our response:** On the issue of the lag period between cognitive testing and vaccine hesitancy ascertainment, there are four brief points to raise here. First, we can show that individual differences in cognitive function are highly stable over a 10-year period. Second, related, little mean decline will take place in the present population over a 10 year period. Third, if there was, on average, a modest amount of general, age-related decline, there would be modest inter-individual differences, such that people would very largely retain their ranking from baseline. Fourth, *all* population characteristics are subject to variation over time and cognition is no exception. As we have shown,1 in resurveys of samples of up to 30,00 individuals in UK Biobank, cognitive function scores (r=0.63, p<0.001, N=9689) have comparable test-retest correlation coefficients compared with cigarette smoking (0.60, p<0.001, N=31,037), blood pressure (0.65, p<0.001, N=19,772), and diabetes (r=0.63, P<0.001, N= 31,037). Additionally, as has been demonstrated empirically,2 this order of correlation may result in regression dilution that is likely to lead to underestimation of risk factor associations. We have now added this information to the text (see red text in discussion).

**Reviewer #1**

This is a straightforward and clear analysis of the association of cognitive ability and vaccine hesitancy in relation to COVID-19, with data collected just as a successful vaccine was announced in the UK. It finds a strong association, with modest attenuation by demographic and health cofounders, except education which has a larger effect.

**Our response:** Thank you for this positive feedback.

I have a few queries about the analysis.

**Our response:** We address these queries in detail below.

The paper shows that there has been significant attrition, but available inverse probability weights to correct for this have not been employed. Since ethnic minorities were oversampled in the original main study, and attrition is likely to be biased, it would be helpful to understand why weighting was not employed and/or if weighting, which would make the study statistically representative of the UK population, makes a difference to the findings presented.

**Our response:** The referee is correct regarding attrition, a point we made ourselves in the limitations section of the original report. In our experience, inverse probability weights have an impact on prevalence estimates but not estimates of the relationship between two variables. We would be happy to demonstrate this empirically in a revised manuscript.

Drew: can we explore the impact of weighting on the main results, please. This would be for the results in green in the attached manuscript (appendix, table 1a).

In addition, there is considerable item missingness when all covariates are included in the model; I assume a complete case analysis was undertaken but I don't think this is explicitly stated. While Figure 1 clearly demonstrates this, a little more discussion of it in the text would be helpful.

**Our response:** Thank you for raising this point. The main results in table 2 are based on a non-missing dataset (N=7361??). We now make that clearer to table and text (see red text).

The sample in wave 6 (nov 2020) of the COVID-1 survey was aged 16 to 95, it is unclear to me how those still in education were scored on the education variable? This may reduce the ranking of the education variable as for younger people it is not based on their final achieved education position, which in turn make affect tis correlation with vaccine hesitancy and cognitive ability. At a minimum how they are treated and the implications of this should be specified. The author may want to consider a different minimum age for the education analysis.

**Our response:** Thank you for raising this point. We agree that, for the small proportion of individuals below the standard age of 21 years for completion of higher education (N=XXXX; X% of the 7361analytical sample in table 2), the educational data are sub-optimal. In sensitivity analyses we therefore restricted the sample to people aged 22 and above when educational attainment was assesses at wave 10 in the Main Survey (XXXX) (N=XXXX). We found that XXXXX

It is a requirement for downloading the data that it is cited. https://www.understandingsociety.ac.uk/documentation/citation

The paper should include the citation for both datasets employed here and include the study acknowledgement.

University of Essex, Institute for Social and Economic Research, NatCen Social Research, Kantar Public. (2020). Understanding Society: Waves 1-10, 2009-2019 and Harmonised BHPS: Waves 1-18, 1991-2009. [data collection]. 13th Edition. UK Data Service. SN: 6614, http://doi.org/10.5255/UKDA-SN-6614-14.

University of Essex, Institute for Social and Economic Research. (2021). Understanding Society: COVID-19 Study, 2020-2021. [data collection]. 8th Edition. UK Data Service. SN: 8644, http://doi.org/10.5255/UKDA-SN-8644-8.

Understanding Society is an initiative funded by the Economic and Social Research Council and various Government Departments, with scientific leadership by the Institute for Social and Economic Research, University of Essex, and survey delivery by NatCen Social Research and Kantar Public. The research data are distributed by the UK Data Service.

**Our response:** These administrative details have been added.

My only small comment on this is the description of the study as a cohort study when in fact it is a panel study. This is relevant to the title, and the methods description in abstract and main text. It is a UK study which is clear when the full name is spelt out in main text but not in title or abstract.

**Our response:** We think this points represents a disciplinary difference in terminology between the social sciences and epidemiology. Panel studies, as made clear using CLOSER materials,[https://learning.closer.ac.uk/learning-modules/introduction/types-of-longitudinal-research/panel-studies/] follow the same individuals over time. In the Dictionary of Epidemiology, they are similarly defined as ...’a series of cross-sectional studies of the same individuals or study sample.’ We therefore regard a panel study as being the same as a cohort study. We have added ‘United Kingdom’ to the abstract; thank you for spotting this omission.

**Reviewer #2**

This is a very great read and timely article. Please consider revision of lines 204-205. Thanks for your efforts.

**Our response:** Thank you for this positive feedback.

The cognitive study results were 10 years old or greater. Cognition can drastically be altered in 10 years, so if there were more recent cognitive results I would have considered using them.

**Our response:** This point was restated by the editor and we therefore also address it above. There are four brief points to raise here. First, we can show that individual differences in cognitive function are highly stable over a 10-year period. Second, related, little mean decline will take place in the present population over a 10 year period. Third, if there was, on average, a modest amount of general, age-related decline, there would be modest inter-individual differences, such that people would very largely retain their ranking from baseline. Fourth, *all* population characteristics are subject to variation over time and cognition is no exception. As we have shown,1 in resurveys of samples of up to 30,00 individuals in UK Biobank, cognitive function scores (r=0.63, p<0.001, N=9689) have comparable test-retest correlation coefficients compared with cigarette smoking (0.60, p<0.001, N=31,037), blood pressure (0.65, p<0.001, N=19,772), and diabetes (r=0.63, P<0.001, N= 31,037). Additionally, as has been demonstrated empirically,2 this order of correlation may result in regression dilution that is likely to lead to underestimation of risk factor associations.

Lines 204-205: The hesitant were also less likely to carry an array of somatic morbidities and be shielding or live with someone who was. (This sentence confused me. Are you saying that the less educated are healthier than the educated participants? Your article is arguing that the less educated are hesitant to be vaccinated, so this sentence contradicts you hypothesis.)

**Our response:** This was simply a commentary on the results in table 1. People who are vaccine hesitant were less likely to have an existing illness or having to shield because of one.

It would been nice to see if prior medical encounters, religion, or mistrust impacted vaccination hesitancy. Additionally, it would be a great recommendation to conduct the same study on males of the same age group. Furthermore, consider expanding ethnicity beyond white and non-white. History of grossly falsified research has caused many to reconsider their stands on vaccines.

**Our response:** We agree that there might be value in exploring other predictors of vaccine hesitancy and this has been done by other research groups using the present dataset.[ref] This includes ethnicity where considerable variation across the groups was apparet.[ref] Just as there is value is using an expansive definition of ethnicity, we also feel that there is much to be gained by expanding work beyond men of a particular age.

I look forward to reading the final product.

**Our response:** Thank you for your interest.

**References**

1. Batty GD, Deary IJ, Gale CR. Pre-pandemic cognitive function and COVID-19 mortality: prospective cohort study. *Eur J Epidemiol.* 2021.

2. Clarke R, Shipley M, Lewington S, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol.* 1999;150(4):341-353.