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Title	Brain structure and function in individuals recovering from COVID-19 after hospitalization or self-isolation: a longitudinal observational study protocol
Authors	Bradley J. MacIntosh, Xiang Ji, J. Jean Chen, Asaf Gilboa, Eugenie Roudaia, Allison Sekuler, Fuqiang Gao, Jordan A. Chad, Aravinthan Jegatheesan, Mario Masellis, Maged Goubran, Jennifer Rabin, Benjamin Lam, Ivy Cheng, Robert Fowler, Chris Heyn, Sandra E. Black, Simon J. Graham
Reviewer 1	Dr. José Alberto González Cáceres
Institution	Instituto De Neurología Y Neurocirugía
General comments (author response in bold)	<p>Considerations</p> <p>It is advisable to define who was considered as “non-infectious participants”. From the context, it is understood that it does not refer to the contagion capacity, but this should be clarified. Is that referring to PCR negative patients? what is different from patients with viral transmission capacity. Prolonged viral RNA detection does not indicate prolonged infectiousness.</p> <p>Author reply: We thank the reviewer for making this valuable comment and have added these details. To address the issue of non-infectious status, we have added one sentence in the Methods under the subheading “COVID-19 status”.</p> <p>Was the follow-up time criterion (s) based on any prior evidence, or was it arbitrarily determined? It is recommended that the criteria be explained.</p> <p>Author reply: We discuss this point in the Interpretation section.</p> <p>“Recruitment is undertaken through the emergency department electronic database, physician referrals, and advertisements in the community and on social media” The time to recovery from COVID-19 is highly variable and depends on age and pre-existing comorbidities in addition to illness severity. The average time from the onset of symptoms to recovery is 2 weeks when the disease has been mild and 3-6 weeks when it has been severe or critical. The moment in the natural history of the disease in which the patients are captured could significantly influence the results of the investigation. Referring to being able to establish an association between whether the findings are due to the disease itself, or to other complications not related to it. These data must be clarified in the protocol, the methodology and the results.</p> <p>Author reply: We added a sentence in the Methods (i.e., pairwise group comparisons) and Interpretation (i.e., time to recover) sections to address these astute points.</p>
Reviewer 2	Dr. Fahad Razak
Institution	University of Toronto Faculty of Medicine
General comments (author response in bold)	<p>This is an excellent and important study. Very well written protocol paper. Congratulations! A few minor suggestions below:</p> <p>1) Page 4 “NeuroCOVID-19 is a longitudinal observational study that is recruiting non-infectious participants in three cohorts: individuals who contracted COVID-19 and were either 1) hospitalized, or 2) self-isolated; and age- and sex-matched controls, 3) with recent flu-like symptoms who tested negative for COVID-19 and were self-isolated.”</p> <p>Author reply: We agree with this suggestion and have revised accordingly.</p>

Phrasing is confusing here, and not sure which group are the “and age- and sex-matched controls” –assuming it is the flu-like illness. Can you please rephrase and just define the three groups simply: Group 1 is ... Group 2 is..., Group 3 is....

Author reply: We rephrased as requested.

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“Linear regression model will be used to test for an association between brain lesions and COVID-19 while accounting for age and sex as covariates.”

If brains lesions are discrete counts bounded by zero (i.e., can’t have less than 0 lesions), I believe other models are perhaps better suited such as a negative binomial or Poisson – suggest consultation with a statistician.

Author reply: This point is helpful and relates to Editor-8 above. The brain vascular lesions are no longer part of the main objective.