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Prospective studies are needed of the neurology and neuropsychiatry of COVID-19: reply

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To the Editor,

We were interested to read the article by Odone and colleagues (1) which described the characteristics of the general COVID-19 literature base. Appraising 10,000 articles published on COVID-19 between January and May of this year, the authors found a majority of secondary opinion pieces, hypothetical reports and individual perspectives, with more than 60% of studies lacking original "primary" data. They concluded that secondary data sources currently dominate the evidence informing clinical and public health decision making.

We are a collaborative group of clinical academics exploring the neurologic and neuropsychiatric manifestations of COVID-19, through a blog for the Journal of Neurology, Neurosurgery, and Psychiatry (2). We perform daily systematic literature searches of PubMed and preprint servers, critique the evolving evidence and maintain a weekly-updated database. We examined our growing database to ask whether the literature, specifically limited to neurological and neuropsychiatric consequences of SARS-CoV-2 infection, showed a similar pattern of results to those of Odone et al.

As of 24th August and excluding pre-clinical mechanistic data we identified 840 studies including a total of 224,741 infected patients. Of these studies, 522 (62.1%) presented primary data - comparing favourably to the report of approximately 40% in the more general study by Odone et al. However, we continued further to examine the broad nature of this primary research. We found that the vast majority of primary studies in our database were retrospective (458/522, 87.7%) with fully two thirds of primary studies comprising single case reports or very small (n<10) case series (348/522, 66.7%) (Table 1).

We would therefore highlight a general lack of prospective research (64/522 primary studies, 12.3%) in studies of neurological or neuropsychiatric outcomes, at present. Among this smaller group of prospective designs, we noticed that studies examining

Table 1. Currently, the literature on the neurology and neuropsychiatry of COVID-19 is predominantly retrospective or secondary.

Total studies	**840**
Primary data	**522**
Retrospective data	458
Case reports	*256*
Small case series (n<10)	*92*
Other, e.g. retrospective case-note	*110*
Prospective data	64
Secondary data	**318**
Meta-analyses	14
Reviews	262
Other secondary data	42

psychiatric outcomes of anxiety, depression, or post-traumatic stress, or neurological symptoms of anosmia or dysgeusia, appear to be relatively more frequent than studies examining other outcomes. This pattern may reflect the relative ease and availability of quick and simple screening tools to evaluate psychiatric symptoms, or smell and taste disturbance, allowing more responsive prospective approaches early in an evolving pandemic.

We also found 14 meta-analyses estimating the prevalence of nervous system symptoms and outcomes with COVID-19. Since these meta-analyses must rely heavily on retrospective and relatively small-scale studies, the stability of their estimates should be prospectively confirmed. This is especially so when one considered that many of the outcomes in these reviews (e.g., delirium, fatigue, anxiety, or symptoms of post-traumatic stress) are also common in critically ill populations generally (3). Longitudinal research including the use of non-COVID-19 critically ill control patients will help greatly to elucidate the additive effect of COVID-19 on nervous system manifestations, above that of being critically ill (4).

Overall therefore, we wish to highlight a clear need for prospective primary studies to evaluate the potential long-term neurological or neuropsychiatric effects of COVID-19. Our analysis likely does not represent the full scale of the literature because our search was limited to a single database. This limitation has led us to explore a 'living' systematic review and meta-analysis, which we hope will provide a more formalised and academic approach to understanding this evolving evidence. Our hypothesis is that over time, the balance will shift towards reporting original data in prospective studies, to better inform our knowledge of the complex neurological and neuropsychiatric manifestations of COVID-19.

Conflict of interest

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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