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.

Sleep Medicine 91 (2022) 282–288

Contents lists available at ScienceDirect

Sleep Medicine

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

Original Article

Coronavirus infections from 2002 to 2021: neuropsychiatric manifestations

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ARTICLE INFO

Article history:
Received 12 March 2021
Received in revised form
25 November 2021
Accepted 25 November 2021
Available online 8 December 2021

Keywords:
COVID-19
Coronavirus
Neuropsychiatry
Depression
Delirium
Psychosis

ABSTRACT

Coronaviruses have been known to infect humans for several decades and there are four endemic subtypes: HCoV (human coronavirus) −229E, -NL63, -OC43 and -HKU1. These mainly cause a mild upper respiratory illness, but occasionally in vulnerable individuals they can result in more severe respiratory disease and, rarely, CNS involvement. Prior exposure to these viruses has also been associated with an increased odds of having a major psychiatric illness. The severe acute respiratory syndrome (SARS), caused by SARS-CoV, started in 2002 and, as well as causing a more severe respiratory phenotype, was also associated with delirium and affective symptoms acutely. Psychosis occurred in about 1% of individuals and was generally thought to be due to corticosteroid administration. The Middle East respiratory syndrome (MERS), caused by MERS-CoV, revealed similar findings. Survivors of both SARS and MERS reported persistent physical and psychological symptoms at least several months after the acute illness. The reported neuropsychiatric symptoms of COVID-19 range from the common symptoms of systemic and upper respiratory infections to severe and disabling conditions. Delirium has been described using varying terminology; as well as being a possible presenting feature of COVID-19, it has also been shown to be a marker of severe disease. Stroke, both ischaemic and haemorrhagic, have been reported to be more common in COVID-19 than in other medical illnesses. Mood and anxiety disorders are likely to be common at follow-up, while psychosis remains rare and controversial. 'Long Covid' is likely to represent a highly clinically and aetiologically heterogeneous group.

1. Introduction

Coronaviruses are globally distributed viruses capable of infecting humans and animals. This article focuses on human coronaviruses (HCoVs) and the possible neuropsychiatric manifestations in an infected host.

At a molecular level, coronaviruses contain a large, single stranded, RNA genome and are enveloped in a capsular structure. Their name reflects their organisation, as the viral membrane resembles a crown (Latin, *corona*) [1]. There are two major types of coronaviruses, namely alpha- and beta-coronaviruses.

Initial descriptions of coronavirus infections date back to the 1960s and seven different human coronaviruses (HCoVs) have been identified (Table 1) with a range of clinical manifestations.

Coronaviruses frequently affect the respiratory system, usually causing coryzal symptoms, but even the common, endemic coronaviruses have been known to cause more severe lower respiratory tract infection in infants, the elderly and the immunocompromised [2].

Coronavirus outbreaks and most notably, the COVID-19 pandemic, also have an extensive socio-economic impact, which may entail financial difficulties, difficulties accessing healthcare, increased access to suicidal means, deprioritisation of mental health services, social isolation, domestic abuse and drug misuse [3]. At a population level, there is some evidence of a widespread negative mental health impact [4]. Several papers have focussed solely on the impact that coronavirus exposure and involvement in a pandemic have on the mental health of multiple groups including healthcare workers [5], children [6] and the elderly [7], suggesting several adverse outcomes. The psychosocial impact extends beyond the individual, as family and friends may be impacted by the illness and loss of loved ones. This article aims to focus exclusively on the neuropsychiatric impact of coronaviruses in infected individuals.

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https://doi.org/10.1016/j.sleep.2021.11.013
1389-9457/

Table 1
Human coronavirus strains.

Structure	Human Coronavirus Strains	Disease
Alphacoronavirus	HCoV-229E	–
	HCoV-NL63	–
Betacoronavirus	HCoV-OC43	–
	HCoV-HKU1	–
	MERS-CoV	Middle East Respiratory Syndrome (MERS)
	SARS-CoV	Severe Acute Respiratory Syndrome (SARS)
	SARS-CoV-2	COVID-19

2. Common coronaviruses

There are a small number of coronaviruses with a global distribution, including 229E, OC43 and NL63. These can also be grouped as they produce a similar clinical syndrome, with 229E and OC43 accounting for approximately 15–29% of cases of the common cold [1]. This is generally mild, but another widely distributed coronavirus, HKU1, can cause more severe symptoms and a small number of fatalities have been reported from subsequent pneumonia [8].

A small number of severe neuropsychiatric outcomes have been observed in the literature. Early literature identified meningitis and seizures as potentially associated with coronavirus infections [9]. These are rare manifestations and febrile seizures predominantly have been observed to affect children [10]. Gaunt et al. describe a patient testing positive for HKU1 developing meningitis and another with OC43 developing seizures [11]. Febrile seizures have been documented elsewhere, including in a study from Hong Kong in which 14% of hospital inpatients with OC43 developed febrile seizures, which rose to 50% in the HKU1 group [12].

In the longer term, two studies from one research group used a case–control design in which patients with and without psychiatric disorder were compared in terms of their seropositivity for IgG antibodies, indicating prior infection with coronavirus subtypes associated with minor respiratory tract disorders. In a study of 257 individuals, Okusaga et al. found that having a mood disorder conferred an odds ratio of 2.72 (95% CI: 1.88 to 3.94) for prior infection with HCoV-NL63 compared to healthy controls [13]. Severance et al. compared 106 individuals with a recent onset of psychotic disorder (affective or non-affective) to 196 control subjects without psychiatric disorder and found higher rates of prior infection with HCoV-HKU1 (OR 1.32, 95% CI: 1.03 to 1.67) and HCoV-NL63 (OR 2.42, 95% CI: 1.25 to 4.66) but not with HCoV-229E or HCoV-OC43 [14].

3. Severe acute respiratory syndrome (SARS)

SARS originated in November 2002 in the Guangdong Province of China and spread through Asia, Europe and North America (Fig. 1) [15]. The outbreak accounted for approximately 8096 cases and 774 fatalities [15]. There is evidence that the pathogenesis of SARS affects multiple organ systems, including the brain [16]; we will explore each major neuropsychiatric manifestation in turn.

3.1. Delirium

Delirium associated with SARS was initially described in case reports [17]. Larger observational studies confirmed the association. A prospective cohort study from Hong Kong, published in 2005 acknowledged that 7% of their 88 included patients, experienced psychiatric manifestations. In two patients, this was acute confusion and a further four experienced affective symptoms. However, this trial included a corticosteroid regime which may have affected psychiatric outcomes [18]. Although the mean age in the above study was 42 years of age, acute neurocognitive impairments in the context of SARS is not unique to adults. A further study from Hong Kong found that six children (15%) exhibited a mild impairment in attention or memory, but this was transient. Again, it is likely that the reasons for any transient cognitive impairment were multifactorial [19] and it is possible that medication treatment is a major factor in such reports, as evidenced by a study from Mackay et al. who identified confusion as an adverse reaction to ribavirin in the treatment of SARS [20].

3.2. Insomnia

Although sleep dysfunction can present variously, most authors have described sleep disturbance using the general term of *insomnia*. A previous systematic review found insomnia to occur in 41.9% (22.5–50.5%) of patients with acute SARS, falling to 12.1% (8.6–16.3%) at follow-up [21]. Qualitative literature from Maunder et al. observed the effects of SARS on patients at a hospital in Toronto. They observed insomnia to be due to a series of factors including, “corticosteroids, anxiety, physical discomfort and hospital routines”. It was noted that patients exhibited anxiety about their insomnia, suggesting there may be an interplay between affective symptoms and sleep [22].

3.3. Mood and anxiety symptoms

Multiple studies have noted the role of anxiety in the acute stages of SARS infection.[18,23,24] One such study from Hong Kong

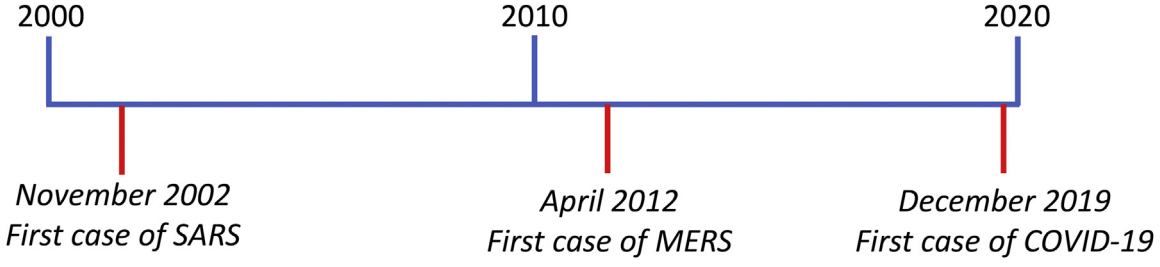

Fig. 1. Timeline of coronavirus cases.

collected data in the first four weeks of SARS infection. Their results indicated that 35% of participants scored in moderate to severe or severe ranges for anxiety or depressive symptoms, although the response rate was only 42.4% with an overrepresentation of women in the final cohort [24].

Affective sequelae have been reported in studies from other geographical locations. Amongst a small group of healthcare workers in Toronto, anxiety was identified as a prominent feature in most patients [23]. However, this was a small and very specific sample making their results difficult to extrapolate.

As well as anxiety, depression has been noted in the literature. [18,19,24] A meta-analysis including four studies of SARS and one of MERS found a prevalence of depression of 14.9% (12.1–18.2%) with low between-study heterogeneity [21].

3.4. Steroid-induced psychosis

Steroid induced psychosis is an uncommon but notable manifestation that has been reported in the literature. An important case–control study from 2004 compared 15 patients with SARS-related psychosis to 30 SARS patients without psychosis. The above cases were identified within a screened population of 1744 patients, suggesting an incidence of 0.9%. 10 cases were clinically diagnosed as steroid-induced mania and 3 as steroid-induced psychosis, suggesting that the major contributor to psychosis was medications rather than the disease itself, although the difference in steroid dose between the two groups was modest [25].

3.5. Long term manifestations

A study from Toronto has posited that “chronic post-SARS” culminates in a cluster of symptoms including fatigue, myalgia, depression and non-restorative sleep, which resembles fibromyalgia and chronic fatigue syndrome [26]. A systematic review and meta-analysis from 2020 identified multiple outcomes across body systems at 6 months post discharge from hospital following either SARS or MERS infection. Psychiatric disease burden was high for depression, anxiety and PTSD; “with pooled estimates of 38.80% (95% CI 30.93–47.31) for post-traumatic stress disorder (PTSD), 33.20% (95% CI 19.80–50.05) for depression, and 30.04% (95% CI 10.44–61.26) for anxiety”. It is important to note that only six studies were identified in the analysis of mental health outcomes and one included patients with MERS infection [27].

4. Middle east respiratory syndrome (MERS)

In comparison to SARS, MERS has caused fewer human cases (2229) with 791 deaths following the 2012 outbreak [15]. The neuropsychiatric literature is therefore sparser.

4.1. Delirium

Delirium has been widely reported in several studies. A small study investigating MERS patients, both survivors and non survivors, observed “altered mentality” in two individuals, amongst a cohort of 30 patients, both of whom died. They suggest altered mental state may be a risk factor for mortality [28].

A larger study by Noorwali et al. provides some support to the above observations. They conducted a retrospective review of MERS cases during a four-month period in 2014, amassing 261 cases. Of these, “altered consciousness” was observed in 53 patients [29]. Saad et al. reported similar findings in their study of 67 symptomatic patients from an outbreak in Saudi Arabia. Of their cohort, 25.7% suffered with confusion [30].

This is further supported by research from Kim et al. who identified 30 patients with confirmed MERS infection. They identified a host of neuropsychiatric manifestations, many of which were likely indicative of delirium: insomnia (7 patients), disorientation (2), impaired memory (2), auditory hallucinations (2) and aggressive outbursts (2). Several patients also met diagnostic criteria for adjustment, anxiety, depressive and acute stress disorders after recovery from delirium. These findings demonstrate the wide variety of possible manifestations of MERS infection and that this may represent a chronic clinical need if such manifestations persist [31].

A systematic review by Rogers et al., identified combined rates of delirium symptoms across SARS and MERS. Interestingly, the review acknowledges that confusion as a neurocognitive manifestation was unexpected given the average age of the populations in the relevant studies: 37·6 years (SD 12·4) and 41·2 years (18·6) [21]. These findings suggest that delirium could be a feature of SARS or MERS infections, regardless of the affected patient's age.

4.2. Mood and anxiety symptoms

Qualitative literature has recognised the prominence of affective symptoms in MERS infection. Interviews conducted by Almutairi et al. with infected healthcare workers found that they reported, “lived moments of traumatic fear and despair” and the article highlights the anxiety participants experienced [32]. Although this was a limited sample in a unique setting, it provides an insight into the lived experience of those suffering from an epidemic viral infection.

This is further supported by research from Jeong et al. from the MERS outbreak in Korea. Amongst their 1692 participants, 36 MERS cases were identified, of whom 47.2% (30.9–63.5) experienced anxiety, compared to only 7.6% (6.3–8.9) of a comparison group that were in isolation but were not infected. Interestingly, this effect was maintained at 4–6 months but to a lesser extent [33].

4.3. Long term manifestations

A case series published in 2016 detailed the neurological sequelae of MERS infection in two patients. One patient developed thrombocytopenia which led to intracerebral haemorrhage and another developed critical illness polyneuropathy. The article caveats that these manifestations were in the context of the complications of prolonged ICU admissions [34].

An interesting article focussing on the MERS outbreak in South Korea in 2015 looked at the relationship between chronic fatigue, depressive symptoms and post-traumatic stress symptoms (PTSSs). They found that fatigue at 12 months post-MERS was associated with prolonged PTSSs at 18 months [35].

Another study from South Korea retrospectively studied the psychological impact. Within the sample of 24 individuals, 70.8% of patients who survived the MERS infection had psychiatric symptoms during admission. In addition, 10 patients (41.7%) received a psychiatric diagnosis; these included adjustment, anxiety, acute stress and depressive disorders. These results should be caveated as this was a retrospective assessment on a small sample size and participants were in quarantine during the assessment [31].

Similar findings were evident in a further study investigating outcomes at 1 year following the MERS outbreak in South Korea. Figures from their study indicate that 54% of participants experienced at least one symptom of PTSD, depression, suicidality or insomnia. Specifically, 42.9% had PTSD, 27% had depression, 22.2% demonstrated moderate suicide risk and 28% significant insomnia [36].

5. COVID-19

The coronavirus pandemic that defined the year 2020 was COVID-19, which originated in Wuhan of the Hubei Province of China in late 2019 [37]. As of 29th September 2021, 232636622 cases have been documented worldwide resulting in 4762089 deaths [38].

The reported neuropsychiatric features of COVID-19 have ranged from common symptoms of systemic and upper respiratory infections (headache, dizziness, fatigue, anosmia and dysgeusia) [39] to severe and disabling neurological and psychiatric disorders, including delirium, cerebrovascular disease, peripheral nerve disorders, psychosis, mood disorders, post-traumatic stress disorder (PTSD) and so-called 'long-COVID'. We provide an overview of the reporting of neuropsychiatric manifestations before examining each of these major issues in turn.

5.1. Overview of neuropsychiatric manifestations

It was recognised early in the outbreak that COVID-19 can manifest with a wide variety of neurological manifestations. This is demonstrated clearly by the UK-wide CoroNerve surveillance study published June 2020. Using a novel case reporting platform, the authors identified 125 patients with detailed data on neurological or psychiatric manifestations, of whom 77 (62%) were cerebrovascular events. Of the 39 with altered mental status, 9 had an unspecified encephalopathy and 7 had encephalitis. Approximately half of reported cases of altered mental status occurred in those under 60 years [40].

Several case reports have also detailed instances of encephalitis, but so far this seems to be a rare event [41,42]. Interestingly, research from a hospital network in Chicago with 509 patients found that independent risk factors for developing neurological manifestations were severe COVID-19 (OR 4.02; 95% CI 2.04–8.89) and younger age (OR 0.982; 95% CI 0.968–0.996), suggesting that such presentations are hallmarks of severe disease and are not restricted, as sometimes conceived, to delirium in the elderly [43].

Definitions of neuropsychiatric complications vary and have massive effects on reported prevalences. Using a broad definition including dizziness, headache, anosmia and dysgeusia has given a prevalence of 36.4% [39]. However, a Spanish study using much tighter criteria that were restricted to major neurological disorders found a rate of only 2.6% [44], although delirium in particular is known to be underdiagnosed in studies relying on case note reviews [45].

5.2. Delirium

Various related terms for an acute confusional state in COVID-19 have been used, including encephalopathy, altered mental status and delirium, which has resulted in non-specific descriptions that are hard to synthesise. Recent consensus guidelines have recommended use of the term *acute encephalopathy* to describe a rapidly developing pathobiological process in the brain, whereas *delirium* should be used to describe a clinical state as defined by DSM-5 [46].

Frequency of delirium in COVID-19 varies by setting and methodology. Larger studies have tended to rely on retrospective review of clinical notes with terms suggestive of delirium, with one study of 20,133 hospitalised patients in the UK finding 'confusion' to be present in 26.7% [47]. Prospective studies, where patients undergo a standardised assessment for delirium, have generally found higher rates; one study of 71 hospitalised patients found delirium to be present in 31 (42%), only 12 of whom had been recognised as such by their clinical team [48]. Moreover, delirium can be a first or only manifestation of COVID-19 in a significant minority of older patients [49].

One study investigating 61 patients admitted to a hospital in Washington observed altered mental state to be the most commonly observed neurological manifestation, affecting 66% of their cohort. Crucially for clinical practice, five of such patients did not have respiratory symptoms [50].

A larger study amongst 12,601 inpatients found that among 8.7% with encephalopathy, there were more medical comorbidities, and this group had a higher likelihood of requiring critical care unit with a higher 30-day mortality [51]. Unsurprisingly, there is evidence that encephalopathy is more common in ITU populations [52]; one such study cited rates of encephalopathy at 84.3% of 140 patients, increasing the burden on critical care services [53]. There are several factors that may be driving the development of delirium in COVID-19. As with any cause of delirium, these range from pre-existing patient factors (such as age and frailty) to direct effects of the illness (including fever, metabolic dysregulation and organ failure), but it is possible that some of the environmental factors that are specific to COVID-19 (isolation, use of personal protective equipment and lack of social interaction) may be contributing [54].

5.3. Cerebrovascular events

Stroke as a consequence of COVID-19 infection has been extensively studied. One systematic review from December 2020 identified 30 studies with a total of 55,176 patients. Their results indicate that the average age of affected patients was 65.5 years and incidence across studies was 1.74% "(95% CI: 1.09%–2.51%)" [55]. Amongst the included studies, several were case series. As such, they are subject to publication bias and results should be interpreted with this in mind. Ischaemic stroke is more common, but intracranial haemorrhage has also been associated with COVID-19 [56]. Stroke can of course have multiple neuropsychiatric consequences, including, but not limited to, depression, anxiety, apathy or psychosis that may require long term psychiatric input [57].

5.4. Guillain-Barre syndrome (GBS)

The possible association of COVID-19 and GBS has been debated throughout the pandemic. Initial case reports drew it to the attention of clinicians around the world [58]. Further publications noted geographical clusters [59]; a large-scale study from 61 Spanish emergency departments spanning 71,904 COVID-19 patients, diagnosed 11 cases of GBS. They acknowledged that the relative frequency of GBS was higher in COVID-19 patients than in non-COVID-19 patients (OR 6.3, 95% CI 3.18–12.5) [60]. However, a UK-based study by Keddie et al. that examined data from the National Immunoglobulin Database found that the incidence of GBS fell between March and May 2020 compared to the same time period in 2016–2019. They recognised the role of lockdown, which not only reduces the transmission of COVID-19 but also other inducing pathogens, such as *Campylobacter jejuni* [61]. Overall, a systematic review from January 2021 offers a cautious conclusion; "GBS may be associated with COVID-19" [62]. At present, there is not sufficient evidence to say for certain, but it is clear that GBS offers a cautionary tale of the risks of interpreting associations from case reports.

5.5. Psychosis

The UK surveillance study previously mentioned found 10 cases of new-onset psychosis [40]. However, this study has been criticised for the potential inclusion of patients with delirium [63], though the original authors have been clear that they do not think

that all the psychotic symptoms in acute COVID-19 can be subsumed into a label of delirium [64]. A review in November 2020 found 42 patients who had developed psychosis alongside COVID-19 infection, but the authors concluded that, while there was biological plausibility, the association failed to meet the Bradford–Hill criteria for causality. Further study of the association, especially as psychosis is a relatively uncommon manifestation, will be necessary to establish the relationship [65].

It is possible that rates of steroid induced psychosis may increase following the RECOVERY trial demonstrating benefit of dexamethasone use [66]. Therefore, the clinical landscape may change rapidly in this area.

5.6. Mood and anxiety disorders

A systematic review published in October 2020 identified only two studies investigating psychiatric symptoms in patients infected with COVID-19. These identified post-traumatic stress symptoms in 96.2% and depressive symptoms in 29.2%. Interestingly, patients who already had a mental health diagnosis reported that their symptoms worsened [67]. This is supported by a study investigating patients who experienced pneumonia during their COVID-19 infection, six weeks after discharge from hospital. Of 101 recruited patients, "HADS scores $\geq$8 for depression were found in 16.6% and in 12.5% for anxiety" [68]. Larger studies are now reporting with one by Taquet et al. including 62,000 individuals with COVID-19, which found mood and anxiety disorders to be more common in COVID-19 than in other common medical illnesses up to 3 months post-diagnosis [69].

5.7. PTSD

A study from February 2020, investigated rates of PTSD at follow up after severe COVID-19 infection; amongst 381 patients, 115 met criteria for PTSD. Those affected were more likely to be female, have a history of psychiatric disorder, have experienced delirium or agitation during their acute illness and have more persistent physical symptoms at follow-up. As a cross sectional study, these results should be interpreted with caution and the acknowledgement that PTSD symptoms may vary over time [70]. Most of the PTSD literature has, however, focused on the general population or those in quarantine, rather than focusing on infected individuals.

5.8. 'Long covid'

'Long Covid' has been a source of much attention both within the media and healthcare. One of the symptoms that appears to be prominent is persistent fatigue which was noted by a study recruiting patients post COVID-19 infection at St James's Hospital in Dublin, Ireland. Of the 128 recruited participants, they found 52.3% reported fatigue at a median follow-up time of 10 weeks. Female patients and those with pre-existing depression or anxiety, were overrepresented in the affected group. This was a cross sectional study design and longitudinal assessment of fatigue symptoms will be necessary to establish the long term course of this manifestation [71]. Even higher rates have been reported in some studies, such as one assessing patients 4–6 weeks following discharged from one of three major London hospitals, which found 69% of participants experienced fatigue [72]. One study of university students suggests that this fatigue is common even among young adults [73].

With regard to the delayed psychological sequelae of COVID-19, one study investigated broad mental health outcomes at NYU Langone Health in the United States via survey. Mental health scores were significantly lower at an average follow-up of 37 days. However, included patients required at least 6 L of oxygen during their hospitalization and 36.8% of respondents needed home oxygen, which was new for 92.9% of them. Furthermore, patients with communication impairment or dementia, those discharged to a hospice or those who were in long term care prior to admission were excluded [74]. This suggests that included participants represent those severely clinically affected by the illness and may represent a narrow sample of those potentially affected. Extrapolating to the general population should be done with caution.

'Long Covid' is a patient-developed term, which covers a range of post-Covid symptoms that span physical and psychological symptoms. Through coining 'long covid', a community of patients have emerged with similar experiences, allowing them to find support from each other. Furthermore, this patient-centred approach allows individuals to feel empowered and involved in their healthcare. This is crucial as qualitative literature in this area suggests patients experience stigma and have "difficulty being taken seriously and achieving a diagnosis" [75]. On the other hand, as 'long covid' is not clinician-developed, it lacks a systematic approach and may actually apply to a highly heterogeneous clinical population with varying aetiologies. In addition, due to the variety of possible symptoms, this may represent a challenge for clinicians, resulting in diagnostic overshadowing.

6. Conclusions

When drawing conclusions from the available literature, it is important to consider the research quality. Case reports have had enormous value in highlighting early neuropsychiatric associations with COVID-19 and continue to be useful in establishing rarer presentations. However, as the story of the association between GBS and COVID-19 demonstrates, these case reports are intrinsically susceptible to reporting bias. There is now a need to promote larger prospective studies. One concern raised by the authors of a systematic review has been the low quality of many studies, including less representative sampling methods and the absence of prespecified analyses [76].

There are many clinical implications from the evidence discussed. There is a clear need to involve psychiatry and neurology specialists in acute COVID-19 and follow up. Furthermore, consideration must be given to the resources required to appropriately support these patients, for example, services for persistent physical symptoms, psychological therapy and neurorehabilitation.

One area of uncertainty lies in the form of reinfection and its impact on neuropsychiatric sequalae. This, alongside, larger, prospective studies, would be a useful direction for future study. Time and robust research will demonstrate the full magnitude of future clinical need.

Funding

JPR is funded by a Wellcome Trust Clinical Research Training Fellowship (102186/B/13/Z).

Credit author statement

AB and JPR designed the manuscript. AB drafted the manuscript, which JPR edited. Both authors approved the final version.

Acknowledgements

Ethical approval not applicable.

Conflict of interest

None declared

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.11.013.

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