

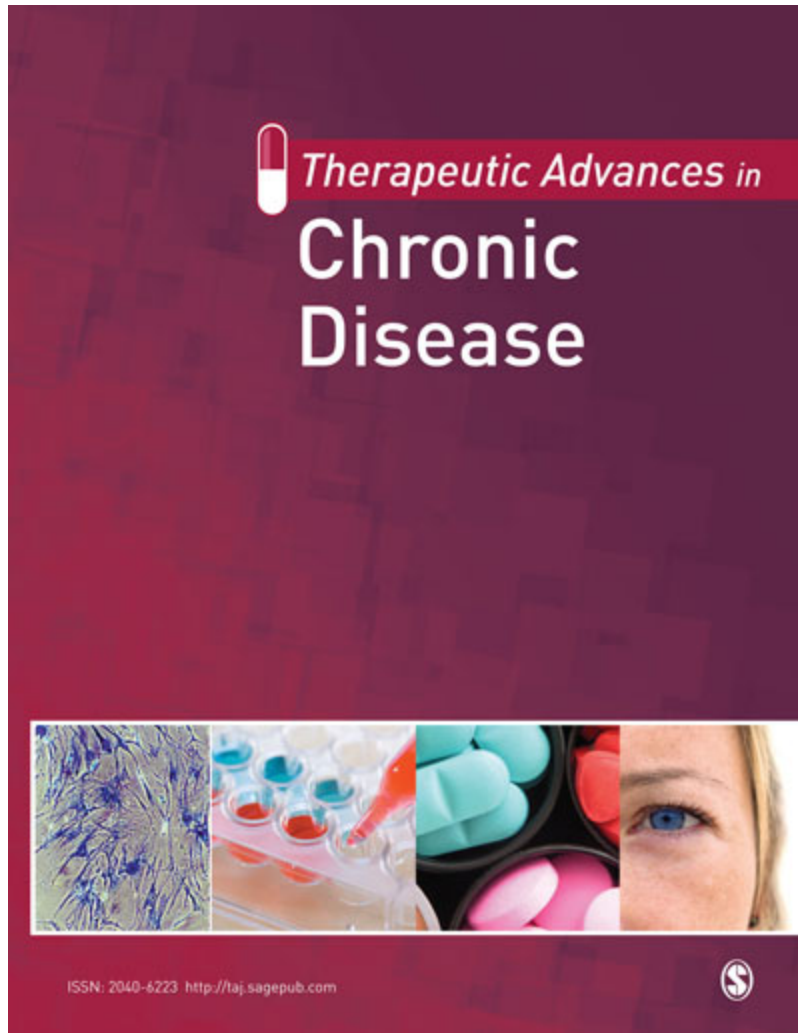
Research Space

Journal article

The neurological symptoms of COVID-19: A systematic overview of systematic reviews, comparison with other neurological conditions and implications for healthcare services

Wildwing, T. and Holt, N.

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The Neurological Symptoms of COVID-19: A Systematic Overview of Systematic Reviews, Comparison with other Neurological Conditions and Implications for Healthcare Services

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<p>Abstract:</p>	<p>Objective: In response to the rapid spread of COVID-19, this paper provides health professionals with better accessibility to available evidence, summarising findings from a systematic overview of systematic reviews of the neurological symptoms seen in patients with COVID-19. Implications of so-called 'Long Covid' on neurological services and primary care and similarities with other neurological disorders are discussed.</p> <p>Methods: Firstly, a systematic overview of current reviews of neurological symptoms of COVID-19 was conducted. Secondly the implications of these findings are discussed in relation to the potential effect on neurological services and the similarities in the experience of patients with COVID-19 and those with other neurological disorders. Forty-five systematic reviews were identified within seven databases, published between 11th April 2020 and 15th October 2020, following a search in June 2020, updated on 20th October 2020.</p> <p>Results: The results indicated that COVID-19 exhibits two types of neurological symptoms; life threatening symptoms such as Guillain Barre Syndrome and encephalitis, and less devastating symptoms such as fatigue and myalgia. Many of these so-called lesser symptoms appear to be emerging as longer-term for some sufferers and have been recently labelled Long Covid. When compared, these less devastating symptoms are very similar to other neurological conditions such as Chronic Fatigue Syndrome (CFS) and Functional Neurological Disorder (FND).</p> <p>Conclusions: Implications for neurological healthcare services in the UK may include longer waiting times and a need for more resources (including more qualified health professionals). There is also a possible change-effect on health professionals' perceptions of other neurological conditions such as CFS and FND. Future research is recommended to explore changes in health professionals' perceptions of neurological symptoms because of COVID-19.</p>

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Manuscripts

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3 **The Neurological Symptoms of COVID-19: A Systematic Overview of Systematic**
4 **Reviews, Comparison with other Neurological Conditions and Implications for**
5 **Healthcare Services**
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12 Keywords: COVID-19, Long Covid, Functional Neurological Disorder, Chronic Fatigue
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14 Syndrome, Neurological Services
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For Peer Review

Abstract

Objective: In response to the rapid spread of COVID-19, this paper provides health professionals with better accessibility to available evidence, summarising findings from a systematic overview of systematic reviews of the neurological symptoms seen in patients with COVID-19. Implications of so-called 'Long Covid' on neurological services and primary care and similarities with other neurological disorders are discussed.

Methods: Firstly, a systematic overview of current reviews of neurological symptoms of COVID-19 was conducted. Secondly the implications of these findings are discussed in relation to the potential effect on neurological services and the similarities in the experience of patients with COVID-19 and those with other neurological disorders. Forty-five systematic reviews were identified within seven databases, published between 11th April 2020 and 15th October 2020, following a search in June 2020, updated on 20th October 2020.

Results: The results indicated that COVID-19 exhibits two types of neurological symptoms; life threatening symptoms such as Guillain Barre Syndrome and encephalitis, and less devastating symptoms such as fatigue and myalgia. Many of these so-called lesser symptoms appear to be emerging as longer-term for some sufferers and have been recently labelled Long Covid. When compared, these less devastating symptoms are very similar to other neurological conditions such as Chronic Fatigue Syndrome (CFS) and Functional Neurological Disorder (FND).

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3 *Conclusions:* Implications for neurological healthcare services in the UK may include longer
4 waiting times and a need for more resources (including more qualified health professionals).
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7 There is also a possible change-effect on health professionals' perceptions of other
8 neurological conditions such as CFS and FND. Future research is recommended to explore
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10 changes in health professionals' perceptions of neurological symptoms because of COVID-
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For Peer Review

Introduction

As of 29th October 2020, over forty-four million people worldwide have been affected by the novel coronavirus COVID-19.¹ It has been found to cause neurological manifestations in up to 50% of patients.² Several systematic reviews have been conducted into the neurological symptoms of COVID-19. However, some reviews focused purely on specific types of symptoms such as olfactory symptoms, whilst others focused on studies only in specific countries, for example a quarter of the studies within the reviews were undertaken in China. It was therefore deemed necessary firstly, to conduct a systematic overview of previously conducted systematic reviews to summarise the neurological symptoms of COVID-19 seen so far.

Secondly, it is becoming clear that COVID-19 affects many patients neurologically, and in some cases, symptoms are persisting. A recent BMJ webinar discussed the emergence of so-called 'Long Covid'.^{3 4} This paper further discusses the concerns about the short and long-term effects of COVID-19 on medical and holistic neurological practice and where future resources will be required.

Thirdly, as COVID-19 is a new disease, the potential similarities with other neurological conditions have not yet been explored in the literature. The authors of this paper identified that many of the neurological symptoms of COVID-19 appear similar to the symptoms of FND. In addition, the BMJ webinar and recent articles^{4 5} discussed the similarities between so-called 'Long Covid' and CFS, as it has become increasingly noticeable that symptoms are similar. Whilst FND is generally regarded as a psychological disorder, the authors of this paper argue that the emerging discussions about supporting patients with 'Long Covid'^{6 7}

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3 should relate to other neurological disorders such as FND and CFS, questioning how these
4 conditions are judged and how treatments are resourced for them as well as for 'Long Covid'.
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11 Neurological services in the UK offer diagnosis and treatment to patients with disorders of
12 the nervous system.⁸ This research is therefore aimed at health professionals and
13 commissioners in the field of neurology and in primary care in the UK. It aims to inform
14 future service provision for those who develop long-term neurological symptoms due to
15 COVID-19; as well as exploring the effect of COVID-19 on health professionals' perceptions
16 towards those with symptoms of FND.
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Methods

A systematic overview of current systematic reviews was conducted to explore the potential impact of the longer-term neurological symptoms of COVID-19. The review protocol was not previously registered to avoid delay in researching and publishing findings related to COVID-19, particularly as the subject is of immediate concern. The implications of the findings of this overview were discussed, including potential effects on neurological and primary care services and on perceptions towards patients with other neurological disorders such as CFS and FND.

To conduct the systematic overview of systematic reviews, the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were followed (Figure 1).⁹ Following these recommendations reduces the risk of bias or selective reporting and demonstrates transparency in the process conducted. In June 2020, updated on the 20th October 2020, the following databases were searched, with date limitations between December 2019 and November 2020: 'PubMed Central', 'Cochrane Database of Systematic Reviews,' 'Ovid' 'ScienceDirect' 'Biomed Central' 'BMJ' and SAGE Journals. The following keywords within the title or abstract were used to conduct each search: 'coronavirus', 'COVID-19', 'SARS-COV-2', 'neurological', 'nervous' and 'review'. For example, PubMed Central was searched using the following search terms: (((COVID-19 OR SARS-COV-2 OR coronavirus[Title]) OR (COVID-19 OR SARS-COV-2 OR coronavirus[Abstract])) AND ((neuro* OR nervous[Title]) OR (neuro* OR nervous[Abstract])) AND ((review[Title] OR (review[Abstract]))). Limitations: Date: 01/12/2019-01/09/2020. Only systematic reviews published in academic journals in English

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3 were retrieved. Reference lists of retrieved systematic reviews were also searched to ensure
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5 literature saturation.
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11 The inclusion criteria consisted of systematic reviews only relating to neurological symptoms
12 seen in patients with COVID-19 since 1st December 2019. Both authors participated through
13 each step of the review independently (screening, eligibility and inclusion). Reviews were
14 screened for relevancy against the inclusion criteria within title and abstract. Full-text reports
15 for all potentially relevant reviews were obtained, including those where there was any
16 uncertainty. The authors screened the full-text reports for relevancy and resolved any
17 disagreement through discussions. Neither of the authors were blind to the journal titles, the
18 authors' of the reviews or institutions.
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33 The Critical Appraisal Skills Programme (CASP) checklist for systematic reviews (2018) was
34 used to establish the quality of each review included within this systematic overview.¹⁰
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36 CASP does not suggest a scoring system, asking only whether each of the ten criterion is
37 achieved. However, for clarity the authors of this review included a 'partly achieved' option.
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39 All included reviews were deemed high quality, as they fulfilled at least seven of the ten
40 criteria. The quality evaluation is set out in Table 1 (Supplementary Material 1). From our
41 evaluation 37 reviews fully achieved nine of the ten criteria. Seven reviews fully achieved
42 eight of the ten criteria, whilst one review fully achieved seven of the ten criteria. None of the
43 reviews met criteria eight: their findings could not be applied to a larger population as they
44 predominantly explored specific symptoms of COVID-19 and/or its effects within a specific
45 population.
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3 All reviews were read in full by both authors. Microsoft Excel was used to compile a list of
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5 all the included reviews and the neurological symptoms mentioned in each. This list was
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7 completed and checked by both authors.
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13 Next, neurological symptoms of COVID-19, CFS and FND were placed into a table to
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15 compare the symptoms, which led to a consideration of the implications for neurological
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17 healthcare services and primary care in the UK, and to the possible change-effect on
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19 perceptions towards CFS and FND.
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Results

A systematic overview of systematic reviews of neurological symptoms of COVID-19

PRISMA guidelines were followed for the search strategy of the systematic overview as seen in Figure 1 (Supplementary Material 2). The database search identified 1,067 papers, with a further 67 papers identified within the reference lists of the included reviews. 61 duplicates were removed. From a total of 1,073 papers, 914 were excluded after title and abstract review for relevance. The remaining 159 papers were reviewed in full. 114 of these were excluded as they did not meet the inclusion criteria (date, study design or methodology). 45 systematic reviews met the inclusion criteria and were included in this overview.

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The 45 systematic reviews were published between 11th April 2020 and 15th October 2020. The characteristics of the reviews can be seen in Table 2 (Supplementary Material 3); the number of relevant studies reviewed within each review, the number of participants in each relevant study and the aims of each study. As mentioned, the CASP checklist was utilised to check for risk of bias in each review.

As can be seen in Table 2, some of the reviews explored issues outside the scope of this review. Within scope of this review, 611 studies relating to neurological symptoms of COVID-19 were reviewed within the 45 reviews. Most of the reviews included the same studies. For instance, Mao et al. (2020) was included in 30 reviews.⁵⁶ Whilst numbers of participants were not always stated, more than 67,529 participants were included across the 611 studies reviewed.

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3 Table 2 also shows how many studies were carried out in each country. As can be seen, a
4 quarter of the studies took place in China (107 studies with at least 27,445 participants).
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6 France, Italy, South Korea, Spain, Sweden, UK and USA also researched more than 2000
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8 participants in each country. This gives an overview of the countries in which neurological
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10 symptoms of COVID-19 are under investigation, although it was not determined whether all
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12 participants were within the country stated. There may also be publication bias as this review
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14 excluded reviews that were not in English.
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23 Throughout the 611 studies, 18 neurological symptoms were described. These are
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25 summarised in Table 3 (Supplementary Material 4). As can be seen, neurological
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27 manifestations of COVID-19 include catastrophic symptoms such as cerebrovascular disease
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29 (CVD), encephalitis and Guillain-Barre Syndrome, which are understandably hugely
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31 concerning and have therefore generated intense discussion and research. COVID-19 has also
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33 been found to cause symptoms such as fatigue, dizziness, ataxia, dysphagia and headache,
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35 which though more benign, can be disabling if they become chronic.
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44 *A comparison between the neurological symptoms of COVID-19 and the most common*
45 *symptoms of FND and CFS*
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49 The most common symptoms experienced by people with FND and those with CFS are
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51 compared with the neurological symptoms of COVID-19 in Table 4 (Supplementary Material
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53 5). The symptoms of FND and of CFS were collated from key NHS sources and DSM-5.^{57 58}
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56^{59 60} Neurological symptoms of COVID-19 include catastrophic symptoms requiring
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58 emergency care such as stroke, brain haemorrhage, encephalitis and Guillain-Barre
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3 Syndrome. However, 12 other neurological symptoms were shown to be similar in COVID-
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5 19 and FND and/or CFS (shaded in grey within Table 4). In fact, every non-catastrophic
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7 symptom of COVID-19, including the much-researched symptom of hyposmia, is also
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9 described as a symptom of FND and/or CFS. Furthermore, most of the symptoms of FND
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11 and CFS, have been experienced by some people with COVID-19 neurological symptoms,
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13 particularly those with Long Covid.
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Discussion

From these results, this paper argues three main points: 1) COVID-19 appears to be becoming chronic for some patients, presenting similar neurological symptoms to FND and to CFS; 2) the long-term neurological effects of COVID-19 may impact neurological and wider health care services; 3) the neurological symptoms seen in COVID-19 may (and should) affect health professionals' perceptions of FND and CFS.

1) Long Covid, FND and CFS present similar neurological symptoms

Long Covid, FND and CFS present similar neurological symptoms; every non-catastrophic symptom of COVID-19 (except for hypogeusia) is described as a symptom of FND and/or CFS. In addition, every symptom of FND (except bladder and bowel issues), and of CFS, (except flu symptoms and heart palpitations) have been experienced by some people with COVID-19. Notably, the main symptoms of Long Covid are increasingly similar to symptoms of CFS (fatigue, inability to concentrate, myalgia, headache).³

2) The impact of these findings on neurological healthcare services and primary care

Echoing concerns raised recently by the British Medical Association,⁶ the findings of this review highlight the impact that short and long-term neurological symptoms of COVID-19 may have on current health services. Symptoms seen in Long Covid such as facial pain, muscle issues, neuralgia, fatigue and insomnia, may become long term and disabling, requiring sustained support from healthcare services such as pain, fatigue and sleep clinics, neurological services and primary care. This is supported by other research which suggests rehabilitation required by patients following COVID-19 infection may be 'very much along

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3 the same lines as existing services but with double the demand'.⁶¹ Consultant-led
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5 neurological services such as chronic fatigue clinics and headache clinics are already
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7 overstretched with a shortage of neurology consultants and long waiting lists.⁶² Neurological
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9 symptoms of Long Covid may increase demand for these clinics and may indicate a need for
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11 more qualified health professionals and specialists in neurology. The effects of COVID-19 on
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13 these services is hard to predict, as the neuropathy, myopathy and sensory deficits of SARS
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15 resolved within three months of recovery.⁴⁶ However, as COVID-19 appears to be becoming
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17 Long Covid for up to 10% of patients,³ support is likely to be required, potentially for a
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19 significant number of people, if their symptoms do not resolve spontaneously.
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28 Additionally, COVID-19 is causing a wider impact on patient populations. For example,
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30 COVID-19 has affected delivery of health care services, through reduction in use of
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32 emergency services during the peak of the pandemic in the UK as patients were worried
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34 about contracting the virus from hospitals.⁶³ There is evidence that some patients with long
35
36 term conditions have improved their self-care techniques, such as better use of medication
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38 and alternative therapies such as physiotherapy, cognitive behavioural therapy, and exercise.
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40 On the other hand, most outpatient appointments and elective surgeries were postponed,
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42 leading in some cases to deaths as an indirect result of COVID-19.⁶⁴ There are now
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44 questions about whether there will be a rebound in demand, potentially overwhelming NHS
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46 services, or whether the reduction in demand can be sustained. Combined with the previously
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48 mentioned potential increase in demand for neurological services, there is likely to be wide
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50 reaching financial implications. This research is therefore useful for aiding future patient
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52 management while helping to develop policies for response to COVID-19 and its critical
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54 outcomes.
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3) *The effect of COVID-19 on perceptions of FND and CFS*

Key sources differ in their description of FND symptoms, indicating that there is no comprehensive list of all FND symptoms.^{57 58 59 60} It is likely that this contributes to health professionals' uncertainty in diagnosing FND.⁶⁵ In addition, patients with both FND and CFS have experienced many years of scepticism from health professionals⁵ with negative consequences, including lack of support and poor access to services often contributing to poor mental health.⁶⁶ In addition, lower value is given to health professionals' role in managing poorly defined symptoms.⁶⁷ FND and CFS, alongside other ambiguous uncertain conditions (e.g. fibromyalgia), are considered amongst the lowest conditions on the hierarchy of importance of conditions.⁶⁸

Conversely, COVID-19 can be quickly and easily diagnosed with a test (leaving aside the possibilities of false results). The authors of this research are concerned that within neurological services, priority may be given to patients who have had COVID-19, who may actually experience some level of prestige because they have survived a disease feared by all, and any neurological symptoms they experience might be automatically accepted, extensively researched and supported, at detriment to other neurological conditions. There is already evidence of this skewing of services, as large sums of money and research at pace are contributing to a greater understanding of long-term symptoms of COVID-19,⁶⁹ and the NHS has declared its intention to provide a COVID-19 rehabilitation service.⁶ Also, there is indication that the presence of Long Covid is unquestionably 'believed' by health professionals, as doctors and other professionals have written about their experiences with it⁵ and are recommending each other's papers.³

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3 However, some patients with emerging Long Covid have similar experiences to those with
4 less accepted conditions, particularly those who were unable to get a test early in the
5 pandemic.⁷⁰ Patients feel doctors dismiss their symptoms, they feel desperate, and disagree
6 with diagnoses of anxiety. As Garner (2020) explained, “Doctors need to stop diagnosing this
7 as anxiety. We have messed up before, lets’ not do it again with long term covid-19 illness.”⁵
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18 It is important to highlight the similarities between symptoms of Long Covid and other
19 conditions, providing education for health professionals, informing future practice and
20 illustrating the need for more funding for neurological services to meet increased demand.
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22 Whilst research and services for COVID-19 are gaining funding, there is a lack of funding
23 and research into understanding, treatment and support for those who suffer from FND and
24 CFS.⁷¹ FND and CFS are likely to have lower prestige than COVID-19, however the
25 realisation that COVID-19 causes neurological symptoms similar to FND and CFS may lead
26 to a potential shift in perceptions towards these conditions. They may be taken more
27 seriously, and more funding may be made available for appropriate neurological services
28 unrelated to the cause of the symptoms.
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45 **Limitations**

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47 Scientific reports centred on neurological effects of COVID-19 are still scarce, and risk of
48 publication bias is high. For example, within the reviews included in this research, a quarter
49 of the studies were undertaken in China (148) and a further quarter in Europe (179). Only
50 three studies were conducted in the African continent and nine were conducted in the South
51 American continent. Despite the status of COVID-19 as a pandemic, research into the
52 neurological effects of COVID-19 so far has not been conducted worldwide.
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3 This systematic review is grounding its results on previous reviews' findings; thus, it is
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5 difficult to assess how reliable some of these results can be, for example many of the reviews
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7 (156) did not state the source country of their findings. Quality assessment has however been
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9 undertaken as described earlier and the reviews deemed high quality. Retrospective and
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11 prospective studies of larger cohorts are necessary to correctly assess nervous system
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13 involvement, which has not been possible yet for COVID-19 as it is a very new disease and it
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15 is unclear how much it mimics other coronaviruses.
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23 **Conclusion and implications for future research**

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26 There is an array of evidence to show that COVID-19 causes neurological symptoms, and
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28 although it is difficult to ascertain how long-term the symptoms may become, there is
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30 increasing evidence of the presence of Long Covid, symptoms persisting beyond three
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32 months. Although this paper is primarily UK focused, these concerns are likely to be similar
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34 in other countries. This research collates the evidence so far and provides insight into the
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36 neurological effects of COVID-19 in relation to FND symptoms. Concerns about the
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38 potential impact of these findings on the delivery of neurological and wider healthcare
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40 services are considered alongside the potential effect COVID-19 may have on perceptions of
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42 neurological symptoms, particularly those relating to FND and CFS. Further research is
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44 recommended to explore whether the neurological symptoms of COVID-19 will improve
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46 acceptance and understanding of FND or whether this will worsen the experience for those
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48 who suffer from FND. Further thought for future planning of health care resources also needs
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50 to be taken into consideration, in light of this pandemic.
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3 **Funding and conflict of interests**
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6 This research received no grant from any funding agency in the public, commercial, or not-
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8 for-profit sectors.
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11 The authors declare that there is no conflict of interest.
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For Peer Review

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Table 1: Quality Assessment using CASP¹⁰ Criteria

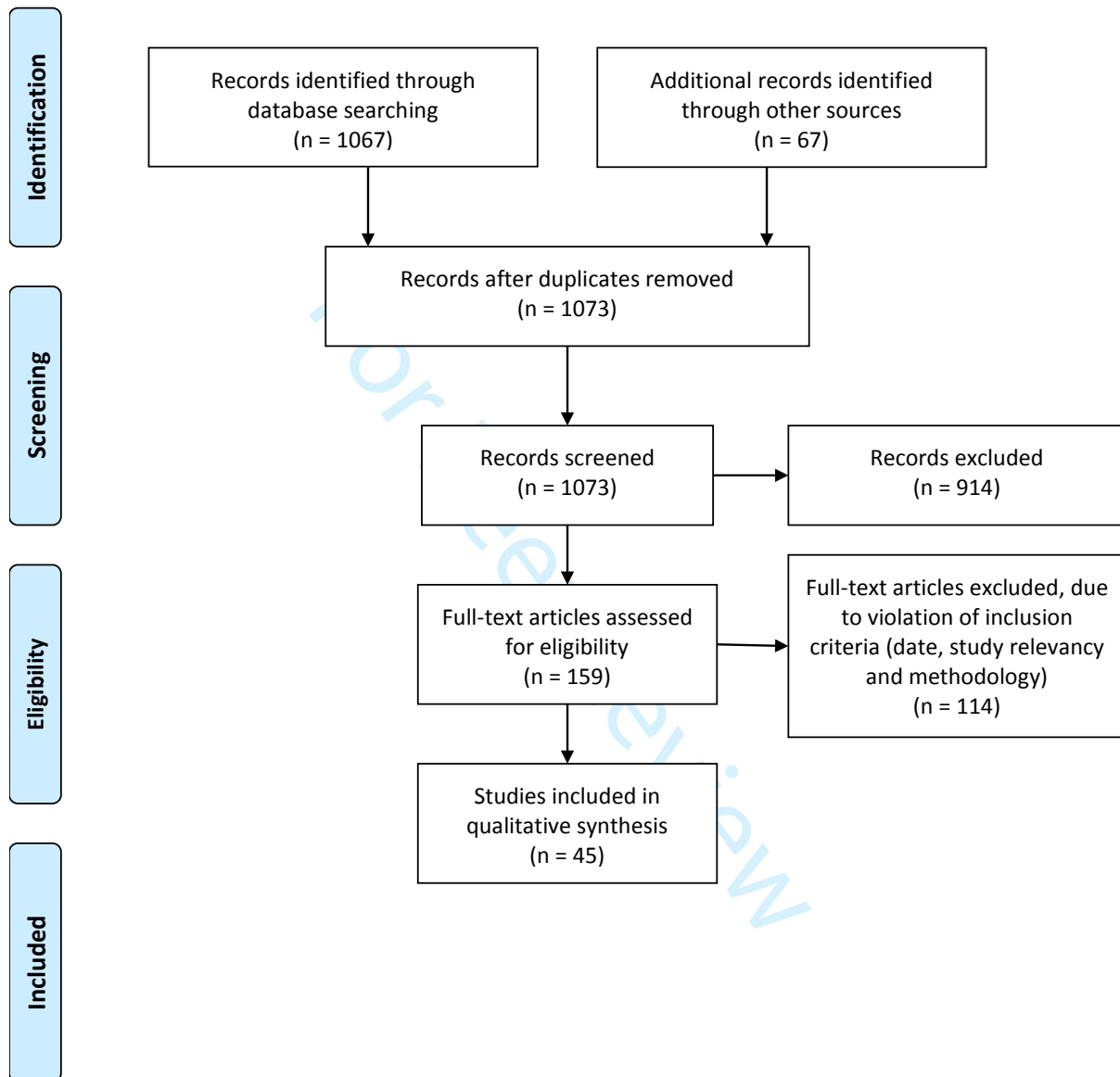
Lead author/ CASP question	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Fully achieved
Abdelaziz ¹¹	y	y	y	partly	y	y	y	n	y	y	8
Abdullahi ¹²	y	y	y	y	y	y	y	n	y	y	9
Abu-Rumeileh ¹³	y	y	y	y	y	y	y	n	y	y	9
Agyeman ¹⁴	y	y	y	partly	y	y	y	n	y	y	8
Almqvist ¹⁵	y	y	y	y	y	y	y	n	y	y	9
Asadi-Pooya ¹⁶	y	y	partly	y	y	y	y	n	y	y	8
Bhatia ¹⁷	y	y	y	y	y	y	y	n	y	y	9
Carrillo-Larco ¹⁸	y	y	y	y	y	y	y	n	y	y	9
Ceravolo ¹⁹	y	y	y	y	y	y	y	n	y	y	9
Collantes ²⁰	y	y	y	y	y	y	y	n	y	y	9
Correia ²¹	y	y	y	y	y	y	y	n	y	y	9
Di Carlo ²²	y	y	y	y	y	y	y	n	y	y	9
Dinakaran ²³	y	y	y	y	y	y	y	n	y	y	9
Fatima ²⁴	y	y	y	y	y	y	y	n	y	y	9
Ghannam ²⁵	y	y	y	y	y	y	y	n	y	y	9
Gittermann ²⁶	y	y	y	y	y	y	y	n	y	y	9
Katal ²⁷	y	y	y	y	y	y	y	n	y	y	9
Katyal ²⁸	y	y	y	y	y	y	y	n	y	y	9
Leonardi ²⁹	y	y	y	y	y	y	y	n	y	y	9
Liguoro ³⁰	y	y	y	y	y	y	y	n	y	y	9
Montalvan ³¹	y	y	y	partly	y	y	y	n	y	y	8
Narula ³²	y	y	y	y	y	y	y	n	y	y	9
Nepal ³³	y	y	y	y	y	y	y	n	y	y	9
Orru ³⁴	y	y	y	partly	y	y	y	n	y	y	8
Paliwali ³⁵	y	y	y	partly	y	y	y	n	y	y	8
Panda ³⁶	y	y	y	y	y	y	y	n	y	y	9
Pinzon ³⁷	y	y	y	y	y	y	y	n	y	y	9
Pousa ³⁸	y	y	y	y	y	y	y	n	y	y	9
Raschetti ³⁹	y	y	y	y	y	y	y	n	y	y	9
Rogers ⁴⁰	y	y	y	y	y	y	y	n	y	y	9
Scoppettuolo ⁴¹	y	y	y	y	y	y	y	n	y	y	9
Sharifan ⁴²	y	y	y	y	y	y	y	n	y	y	9
Taherifard ⁴³	y	y	y	y	y	y	y	n	y	y	9
Tan ⁴⁴	y	y	y	y	y	y	y	n	y	y	9
Trevisanuto ⁴⁵	y	y	y	y	y	y	y	n	y	y	9
Tsai ⁴⁶	y	y	y	y	y	y	y	n	y	y	9
Tsivgoulis ⁴⁷	y	y	y	partly	y	y	y	n	y	y	8
Uncini ⁴⁸	y	y	y	y	y	y	y	n	y	y	9
Valiuddin ⁴⁹	y	y	y	y	y	y	y	n	y	y	9
Vonck ⁵⁰	y	y	y	y	y	y	y	n	y	y	9
Wang ⁵¹	y	y	y	y	y	y	y	n	y	y	9
Werner ⁵²	y	y	y	y	y	y	y	n	y	y	9
Whittaker ⁵³	y	y	y	partly	y	y	y	n	y	y	8
Wilson ⁵⁴	y	y	partly	partly	y	y	y	n	y	y	7
Zahra ⁵⁵	y	y	y	y	y	y	y	n	y	y	9

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- Q1 Did the review address a clearly focused question?
- Q2 Did the authors look for the right type of papers?
- Q3 Do you think all the important, relevant studies were included?
- Q4 Did the review's authors do enough to assess quality of the included studies?
- Q5 If the results of the review have been combined, was it reasonable to do so?
- Q6 What are the overall results of the review? (are they clear?)
- Q7 How precise are the results?
- Q8 Can the results be applied to the local population?
- Q9 Were all important outcomes considered?
- Q10 Are the benefits worth the harms and costs?

For Peer Review

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA)
flow diagram.



PRISMA statement checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table 2: Characteristics of the reviews and number of studies in each country

First author	No. of studies referenced within each review*	No. of participants within each review*	Aim of review
Abdelaziz ¹¹	4 (25)	217 (334)	This review of the literature analyses how HCoVs, in general, and SARS-CoV-2, in particular, affect the nervous system, highlights the various underlying mechanisms, addresses the associated neurological and psychiatric manifestations, and identifies the neurological risk factors involved.
Abdullahi ¹²	60	10314 (11069)	[T]o summarize the evidence on the neurological and musculoskeletal symptoms of the disease. This may help with early diagnosis, prevention of disease spread, and treatment planning.
Abu-rumeileh ¹³	52	58 (73)	[T]o provide a comprehensive and updated overview of all case reports and series of COVID-19-related GBS to identify predominant clinical, laboratory, and neurophysiological patterns and to discuss the possible underlying pathophysiology.
Agyeman ¹⁴	24	8438	To estimate the prevalence of olfactory and gustatory dysfunctions (OGDs) among patients infected with novel coronavirus disease 2019 (COVID-19). ¹
Almqvist ¹⁵	41 (378)	11509 (14418)	[T]o systematically summarize neurological and neuroimaging manifestations of all known HCoVs in order to provide possibilities to predict short- and long-term neurological complications of COVID-19.
Asadi-Pooya ¹⁶	6	765 (not stated)	[To] discuss the evidence on the occurrence of central nervous system (CNS) involvement and neurological manifestations in patients with COVID-19.
Bhatia ¹⁷	30	115	[T]o report the characteristics of stroke in patients with COVID-19.
Carrillo-Larco ¹⁸	8	12	[T]o summarize the main features of patients with GBS and COVID-19.
Ceravolo ¹⁹	18 (36)	346 (not stated)	[T]o gather and present the current evidence informing rehabilitation of patients with COVID-19 and/or describing the consequences due to the disease and its treatment.
Collantes ²⁰	47 (49)	6094 (6335)	[T]o determine the neurological manifestations and complications, including laboratory findings, and outcomes among patients with COVID-19 101 infection.
Correia ²¹	4 (7)	329 (409)	To describe the main neurological manifestations related to coronavirus infection in humans.
Di Carlo ²²	19	6958 (12157)	[T]o analyse the overall rate of neurologic symptoms among COVID-19 patients. Secondary objective was to compare the results between patients with severe and non-severe infection.
Dinakaran ²³	31 (12)	2552 (399)	[To] report the available evidence of neuropsychiatric morbidity during the current COVID-19 crisis. The authors also discuss the postulated neuronal mechanisms of the corona virus infection sequelae.
Fatima ²⁴	6	39	[T]o determine the aetiology, underlying risk factors, and outcomes among patients with COVID-19 presenting with stroke.
Ghannam ²⁵	43 (42)	314 (82)	To clarify the neurological complications of SARS-CoV-2 infection including the potential mechanisms and therapeutic options.
Gittermann ²⁶	24	30	[T]o analyse the available evidence on [the] ... symptoms of Guillain-Barré syndrome associated with COVID-19 ... in the adult population.

Katal ²⁷	21 (28)	681 (not stated)	[To] systematically review ... the available imaging findings of patients diagnosed with neurological symptoms associated with coronavirus infections.
Katyal ²⁸	11	16	[To] analyse ... the current literature on neuromuscular complications associated with SARS-COV-2 and highlighted possible mechanisms of neuromuscular invasion.
Leonardi ²⁹	9 (29)	510 (not stated)	[To examine] neurological manifestations associated with COVID-19
Liguoro ³⁰	11 (65)	34 (7480)	[T]o systematically review main clinical characteristics and outcomes of SARS-CoV-2 infections in paediatric age.
Montalvan ³¹	20 (67)	749	To review the neurological aspects of SARS-cov2 and other coronavirus, including transmission pathways, mechanisms of invasion into the nervous system, and mechanisms of neurological disease.
Narula ³²	11	13	[To] review ... current literature on seizures linked with SARS-COV 2 infection
Nepal ³³	37	3152	[T]o inform and improve decision-making among the physicians treating COVID-19 by presenting a systematic analysis of the neurological manifestations experienced within these patients.
Orrù ³⁴	87	6890	[To review] neurological complications ... of SARS-COV-2
Paliwali ³⁵	80	>15858	[To] focus ... on the neuromuscular manifestations of SARS-CoV-2 infection.
Panda ³⁶	26	3707	[T]o determine neurological manifestations of COVID-19.
Pinzon ³⁷	33	7113 (7559)	To conduct a systematic review and meta-analysis on the neurologic characteristics in patients with COVID-19.
Pousa ³⁸	28	199	[T]o summarize the most common extrapulmonary manifestations in paediatric patients with COVID-19, as well as to discuss clinical, epidemiological, and pathophysiological aspects of these clinical presentations in children.
Raschetti ³⁹	74	176	[T]o clarify the transmission route, clinical features and outcomes of ... SARS-CoV-2 ... in neonates.
Rogers ⁴⁰	12 (72)	1048 (3559)	[T]o assess the psychiatric and neuropsychiatric presentations of SARS, MERS, and COVID-19.
Scoppettuolo ⁴¹	40 (42)	1640 (903)	[T]o provide a clinical approach of SARS-CoV-2 neurological complications based on the direct or indirect (systemic/ immune-mediated) role of the SARS-CoV-2 in their genesis.
Sharifan ⁴²	177 (208)	17595 (not stated)	To summarize available information regarding the potential effects of different types of CoV on the nervous system and describes the range of clinical neurological complications that have been reported thus far in COVID-19.
Taherifard ⁴³	21 (22)	489 (57)	[T]o systematically review the neurological complications in patients with SARS-CoV-2 infection and the methods used to diagnose both neurological complications and coronavirus infection.
Tan ⁴⁴	37 (39)	4720 (135)	[T]o characterize the clinical characteristics, neuroimaging findings, and outcomes of AIS [Acute ischemic stroke] in COVID-19 patients.
Trevisanuto ⁴⁵	26	44	To summarise currently reported neonatal cases of SARS-CoV-2 infection.
Tsai ⁴⁶	36 (142)	3116 (not stated)	[To r]eview and integrate the neurologic manifestations of the Coronavirus Disease 2019 (COVID-19) pandemic, to aid medical practitioners who are combating the newly derived infectious disease.
Tsivgoulis ⁴⁷	13 (not stated)	1641 (not stated)	[T]o present the neurological manifestations associated with SARS-CoV-2 infection and COVID-19. ... We also evaluated the impact of the COVID-19 pandemic on the health care of neurological patients.

1 2 3 4	Uncini ⁴⁸	33	21 (42)	[T]o clarify the clinical and electrophysiological phenotype, to discuss, on the basis of the available data, whether the disease mechanism could be parainfective or post-infective and to speculate on the possible pathogenesis.
5 6 7	Valiuddin ⁴⁹	26	>61	[To] update the clinical manifestations of COVID-19 concentrating on the neurological associations that have been described, including broad ranges in both central and peripheral nervous systems.
8 9 10	Vonck ⁵⁰	21 (20)	3575 (3423)	[T]o perform a review to describe neurological manifestations in patients with COVID-19 and possible neuro-invasive mechanisms of Sars-CoV-2.
11 12 13 14	Wang ⁵¹	41	4345 (not stated)	[T]o systematically collect and investigate the clinical manifestations and evidence of neurological involvement in COVID-19.
15 16 17	Werner ⁵²	14 (not stated)	3351 (not stated)	[To] conduct ... a review of the reported data for studies concerning COVID-19 pathophysiology, neurological manifestations, and neuroscience provider recommendations and guidelines.
18 19	Whittaker ⁵³	32 (31)	2582 (2504)	[To review] the virus' effects systemically, including that of the nervous system.
20 21 22 23 24 25	Wilson ⁵⁴	10	330 (not stated)	[T]o evaluate and summarize the current status of the COVID-19 literature at it applies to neurology and neurosurgery. Neurological symptomatology, neurological risk factors for poor prognosis, pathophysiology for neuro-invasion, and actions taken by neurological or neurosurgical services to manage the current COVID-19 crisis are reviewed.
26 27 28	Zahra ⁵⁵	23	12314	[T]o investigate the diagnostic value of symptoms of anosmia and dysgeusia for COVID-19.

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*Many reviews referenced the same papers, in some cases reviews stated a different number of studies than were referenced within the review, some reviews did not state no. of participants, or total no. of participants, (no. in brackets is total no. of studies/participants where the review included studies not relevant to this review, e.g. reviews of symptoms of other coronaviruses, or no. stated differed from no. found), when reviews differed in their report of participants nos. within the same study a consensus was assumed

Country	No. studies in total	No. participants in total (where stated)	No. studies where no. of participants were not stated (within reviews)
Austria	1	1	
Bangladesh	1	7	
Belgium	4	134	
Brazil	6	256	2
Canada	3	135	1
China	148	27445	12
Europe	2	1837	
France	29	2569	4
France/Spain	1	1	
France/Switzerland	1	6	
Germany	11	188	1
Hong Kong	1	50	
India	6	99	
Indonesia	1	1	
Iran	20	100	5
Israel	2	170	
Italy	61	3708	7
Japan	3	3	
Kuwait	1	2	
Latin America	1	6	
Mexico	2	2	
Morocco	1	1	
Netherlands	4	447	1
Norway	1	2	
Poland/USA	1	u/k	1
Peru	1	1	
Romania	1	126	
Russia	1	1	
Saudi Arabia	2	2	
Singapore	1	870	
South Korea	5	3276	
Spain	24	5393	6
Sudan	1	1	
Sweden	2	2441	
Switzerland	7	17	1
Thailand	1	u/k	1
Turkey	11	176	
United Arab Emirates	2	1	1
United Kingdom	19	4916	2
USA	65	11004	11
Country not stated	156	2134	69
Total: 37 different countries (+ 3 dyads)	611 novel studies	more than 67529 participants	125 studies where participants could not be counted

Table 4: Neurological symptoms of COVID-19

Review authors (1st author) who discussed the named symptoms	Symptom																	
	Acute CVD (a)	Altered Mental Status (b)	Changes to smell and taste	Dizziness	Dysphagia	Encephalitis (c)	Fatigue	Guillain-Barre syndrome (d)	Headache	Mental Health Issues (e)	Muscle Issues (f)	Myelitis	Neuralgia/ Polyneuropathy	Ondines Curse (g)	Polynuritis Cranialis	Seizure (h)	Sensory Disturbances (i)	Sleep issues (j)
Abdelaziz ¹¹	x	x	x	x					x		x		x			x		
Abdullahi ¹²	x	x	x	x					x		x		x			x	x	
Abu-Rumeileh ¹³			x		x		x				x		x		x			
Agyeman ^{14*}			x*															
Almqvist ¹⁵	x	x	x	x		x	x	x	x	x	x				x	x		x
Asadi-Pooya ¹⁶	x	x		x					x		x					x		
Bahtia ^{17*}	x*																	
Carrillo ^{18*}								x*										
Ceravolo ¹⁹	x				x		x	x			x		x		x			
Collantes ²⁰	x			x				x	x		x							x
Correia ²¹	x	x	x	x		x			x		x		x			x		
Di Carlo ²²	x		x	x					x		x							
Dinakaran ²³	x	x	x	x		x	x	x	x	x	x				x	x		x
Fatima ^{24*}	x*																	
Ghannam ²⁵	x			x		x	x	x	x		x		x			x		x
Gittermann ^{26*}			x					x*			x		x					
Katal ²⁷	x	x		x	x	x	x		x		x	x				x	x	
Katyal ²⁸			x					x			x	x			x			
Leonardi ²⁹	x	x	x			x			x		x			x		x	x	
Liguoro ³⁰							x											
Montalvan ³¹	x	x	x			x	x	x	x		x		x			x		
Narula ^{32*}		x				x			x	x	x					x*		
Nepal ³³	x	x	x	x	x	x		x	x		x	x				x		
Orru ³⁴	x	x	x	x		x		x	x		x		x			x	x	
Paliwali ³⁵		x	x				x	x	x		x		x					
Panda ³⁶			x			x	x	x	x		x					x		
Pinzon ³⁷	x	x		x					x		x		x			x	x	
Pousa ³⁸			x						x		x					x		
Raschetti ³⁹											x							
Rogers ⁴⁰	x	x		x		x			x	x					x			x
Scoppettuolo ⁴¹	x		x			x		x			x	x	x	x	x	x		
Sharifan ⁴²	x	x	x	x		x		x	x	x	x	x				x	x	
Taherifard ⁴³	x	x				x	x	x	x		x				x	x		
Tan ^{44*}	x*																	
Trevisanuto ⁴⁵																x		
Tsai ⁴⁶	x	x	x	x		x		x			x		x			x		
Tsivgoulis ⁴⁷	x	x	x	x		x	x	x	x		x				x			

1	Uncini ⁴⁸		X	X					X			X		X				X	
2	Valiuddun ⁴⁹	X					X		X			X	X	X			X		
3	Vonck ⁵⁰	X	X	X	X	X	X		X	X		X		X		X	X	X	
4	Wang ⁵¹		X	X	X	X	X	X	X	X		X	X	X			X	X	
5	Werner ⁵²	X	X	X	X					X		X		X			X	X	
6	Whittaker ⁵³	X	X	X	X		X		X	X		X					X	X	
7	Wilson ⁵⁴	X	X	X	X		X			X							X		
8	Zahara ^{55*}			X*															

11 *These studies specifically looked only at these symptoms

12 (a) incl. strokes and blood clots thought to cause stroke

13 (b) incl. confusion

14 (c) incl. meningitis, encephalopathy

15 (d) incl. Miller Fisher Syndrome

16 (e) incl. suicidal ideation, psychosis, anxiety, depression

17 (f) incl. ataxia, dystonia (specifically sustained upward gaze, dystonic bilateral leg extension, tongue deviation), hypertonia,
18 hypotonia, myalgia, myasthenia gravis, muscle injury, muscle weakness, spasms

19 (g) fatal respiratory failure in sleep

20 (h) incl. epilepsy

21 (i) incl. amblyopia

22 (j) incl. insomnia

Table 54: Comparison between neurological symptoms in COVID-19, FND and CFS

Neurological symptoms in:		
COVID-19	FND	CFS
Acute CVD (a)	no	no
Encephalitis (c)	no	no
Guillain-Barre syndrome (d)	no	no
Myelitis	no	no
Ondines Curse (g)	no	no
Polyneuritis cranialis	no	no
no	Bladder or bowel issues	no
no	no	Chronic sore throat or sore glands that are not swollen
no	no	Flu-like symptoms
no	no	Heart palpitations
Altered mental status (b)	no	Problems thinking, remembering or concentrating
Dizziness	Dizziness	Dizziness
Dysphagia	Dysphagia	no
Facial pain	Facial pain & spasms	no
Fatigue	Fatigue	Fatigue
Headache	Headaches or migraines	Headaches
Hyposmia and/or hypogeusia	Olfactory symptoms	no
Mental Health Issues (e)	Personality changes (e.g. irritability, depression)	no
Muscle Issues (f)	Movement disorders, limb weakness, speech symptoms (e.g. whispering, slurring or stuttering)	Muscle or joint pain
Neuralgia / polyneuropathy	Altered sensation (e.g. numbness, pain)	no
Seizure (h)	Altered awareness episodes (e.g. dissociative or non-epileptic seizures, faints)	no
Sensory Disturbances (i)	Visual symptoms (e.g. loss of vision, double vision, seeing flashing lights) and hearing loss	no
Sleep issues (j)	Sleep problems	Sleep problems

*These studies specifically looked only at these symptoms

(a) incl. strokes and blood clots thought to cause strokes

(b) incl. confusion

(c) incl. meningitis

(d) incl. Miller Fisher Syndrome

(e) incl. suicidal ideation, psychosis, anxiety, depression

(f) incl. myalgia, muscle injury, ataxia, spasms, dystonia

(g) fatal respiratory failure in sleep

(h) incl. epilepsy

(i) incl. amblyopia

(j) incl. insomnia