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Prevalence and Trajectories of Post-COVID-19 Neurological Manifestations: A Systematic Review and Meta-Analysis

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Abstract
Introduction: The aim of this systematic review and meta-analysis was to evaluate the prevalence of thirteen neurological manifestations in people affected by COVID-19 during the acute phase and at 3, 6, 9 and 12-month follow-up time points. ***Methods:*** The study protocol was registered with PROSPERO (CRD42022325505). MEDLINE (PubMed), Embase, and the Cochrane Library were used as information sources. Eligible studies included original articles of cohort studies, case-control studies, cross-sectional studies, and case series with ≥5 subjects that reported the prevalence and type of neurological manifestations, with a minimum follow-up of 3 months after the acute phase of COVID-19 disease. Two independent reviewers screened studies from January 1, 2020, to June 16, 2022. The following manifestations were assessed: neuromuscular disorders, encephalopathy/altered mental status/delirium, movement disorders, dysautonomia, cerebrovascular disorders, cognitive impairment/dementia, sleep disorders, seizures, syncope/transient loss of consciousness, fatigue, gait disturbances, anosmia/hyposmia, and headache. The pooled prevalence and their 95% confidence intervals were calculated at the six pre-specified times. ***Results:*** 126 of 6,565 screened studies fulfilled the eligibility criteria, accounting for 1,542,300 subjects with COVID-19 disease. Of these, four studies only reported data on neurological conditions other than the 13 selected. The neurological disorders with the highest pooled prevalence estimates (per 100 subjects) during the acute phase of COVID-19 were anosmia/hyposmia, fatigue, headache, encephalopathy, cognitive impairment, and cerebrovascular disease. At 3-month follow-up, the pooled prevalence of fatigue, cognitive impairment, and sleep disorders was still 20% and higher. At six- and 9-month follow-up, there was a tendency for fatigue, cognitive impairment, sleep disorders, anosmia/hyposmia, and headache to further increase in prevalence. At 12-month follow-up, prevalence estimates decreased but remained high for some disorders, such as fatigue and anosmia/hyposmia. Other neurological disorders had a more fluctuating occurrence. ***Discussion:*** Neurological manifestations were prevalent during the acute phase of COVID-19 and over the 1-year follow-up period, with the highest overall prevalence estimates for fatigue, cognitive impairment, sleep disorders, anosmia/hyposmia, and headache. There was a downward trend over time, suggesting that neurological manifestations in the early post-COVID-19 phase may be long-lasting but not permanent. However, especially for the 12-month follow-up time point, more robust data are needed to confirm this trend.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been the most severe since the 1918 influenza pandemic [1] and involves a complex disease phenotype that is characterised by, among others, different neurological signs, symptoms and disorders in the acute phase of the disease [2–7]. Additionally, post-acute neurological symptoms, signs, and diagnoses have been documented in an increasing number of people with COVID-19 [8–10].

A major pitfall in studying these neurological manifestations is the considerable heterogeneity in COVID-19 research approaches resulting from different study designs, including study populations and their settings, applied methodology, observation periods, and endpoints [1–10], partly due to the urgency with which most COVID-19 research had to be conducted. This has led to an unclear picture of the post-acute neurological manifestations of COVID-19. Despite the substantial sample sizes achieved by some studies and international registries, only the combination of multiple studies from different settings with different neurological signs, symptoms, and disorders will provide insight into the trajectory of the neurological signature of post-COVID-19 manifestations. Studies have reported that neurological manifestations are highly prevalent, but they were evaluated as a whole and not broken down by individual neurological sign, symptom, or disorder [11, 12]. To date, only four systematic reviews have evaluated the prevalence and type of selected neurological manifestations after the acute phase of COVID-19, and only up to the first 6 months after the acute phase [11–14]. Therefore, the aim of this systematic review and meta-analysis was to evaluate the prevalence of thirteen neurological manifestations in people affected by COVID-19 during the acute phase and at 3, 6, 9, and 12 months of follow-up.

Methods

Study Design

A systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. The study was

Table 1. Criteria for study inclusion and exclusion

	Inclusion criteria	Exclusion criteria
Study design	Cohort studies, case-control studies, cross-sectional studies, case series with ≥5 subjects	Review studies, case reports, case series with <5 subjects, animal studies, autopsy studies, duplicate studies
Participants	Subjects with COVID-19 disease, diagnosed by clinical criteria or laboratory parameters	Subjects in whom a COVID-19 diagnosis could not be confirmed
Control group (not mandatory)	Presence of a control group of subjects without COVID-19 not mandatory	Absence of a control group of subjects without COVID-19 was not an exclusion criterion.
Evaluated outcomes	Report on the prevalence and type of persistent or new neurological manifestations during follow-up	No data on the prevalence or type of persistent or new neurological manifestations after the acute phase of COVID-19
Follow-up	Minimum follow-up of 3 months, in accordance with the WHO definition of post-COVID-19 condition: "the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection" [16]	No follow-up data or follow-up shorter than 3 months after the initial SARS-CoV-2 infection
Publication date	Studies published after January 1, 2020	Not applicable

registered in the PROSPERO database (CRD42022325505). All study authors reviewed the study protocol and gave their feedback prior to its registration.

Pre-Specified Criteria for Study Inclusion

Inclusion and exclusion criteria were pre-specified (Table 1) [16], and studies were assessed according to the PROSPERO protocol.

Data Sources, Search Date, and Search Strategy

The data sources for this review were MEDLINE (PubMed), Embase, and the Cochrane Library. The reference lists of the included studies were also screened for studies meeting the inclusion/exclusion criteria. Unpublished studies and grey literature sources were not included. The publication dates for the literature search were initially from January 1, 2020, to May 15, 2021, and later were updated to June 16, 2022. There were no language restrictions, and studies in languages other than English were translated by native speakers. The full search strategies for each database are available in the online supplementary appendix (for all online suppl. material, see https://doi.org/10.1159/000536352). The search was conducted by a professional librarian from the Mario Negri Institute.

Study Selection Process

The study selection process is described in Figure 1. The abstract of each article was independently assessed by two raters who were blind to each other's decisions. The full text of the articles that fulfilled the inclusion/exclusion criteria outlined in Table 1 was subsequently evaluated by two raters. If an article was excluded, the reasons for exclusion were classified according to a series of pre-specified exclusion criteria (see Table 1 above and online suppl. Table 1). The online platform Rayyan.ai [17] was used to automate the process. Disagreements were resolved by discussion and the participation of a third peer. A total of eight groups of researchers with expertise in neurology and COVID-19 screened the studies and participated in a training session on the Rayyan platform (M.A.L., G.G., E.W., A.S.W., J.A.F., AHK, B.B., F.K.H., D.G.-A., A.V., K.P., A.G., A.S.L., F.M., R.H., L.C., E.S., C.A., M.L., A.F., A.M., A.M., KTT, M.P.). Duplicates were eliminated in Rayyan and manually during the study screening phase.

Data Extraction Process

Information from each study was independently reviewed and entered into the data extraction table by one of the two raters who had screened the full text of the study and was subsequently validated for accuracy by the second rater. All records were additionally reviewed and validated by the core group members (G.G., E.W., D.G.-A., M.A.L., A.S.W.). Information was collected by using a standardised spreadsheet, with pre-specified responses for some categories. Details and definitions for all variables were listed in the spreadsheet. Articles reporting on the same study cohort but with different follow-up evaluations at different time points were merged. A log was kept to track all disagreements and how these were resolved. The data extraction table with definitions can be found in the supplementary appendix (online suppl. Table 1). Disagreements were solved by discussion between the core group and the raters involved until consensus was reached.

All variables were pre-defined by consensus within the core group (G.G., E.W., D.G.-A., M.A.L., A.S.W.), and response possibilities were clearly formulated and limited. The main domains for data extraction were general information about the studies, demographic characteristics of the study population, quality assessments, pre-acute phase (pre-COVID-19 comorbidities), acute phase (period during which signs/symptoms of infection were present), and follow-up at 3, 6, 9, and 12 months, whenever available. Information about the prevalence and type of neurological manifestations was consistent across all pre-specified time points (pre-COVID-19, acute phase of COVID-19, and follow-up time points). When studies reported data at a time point different

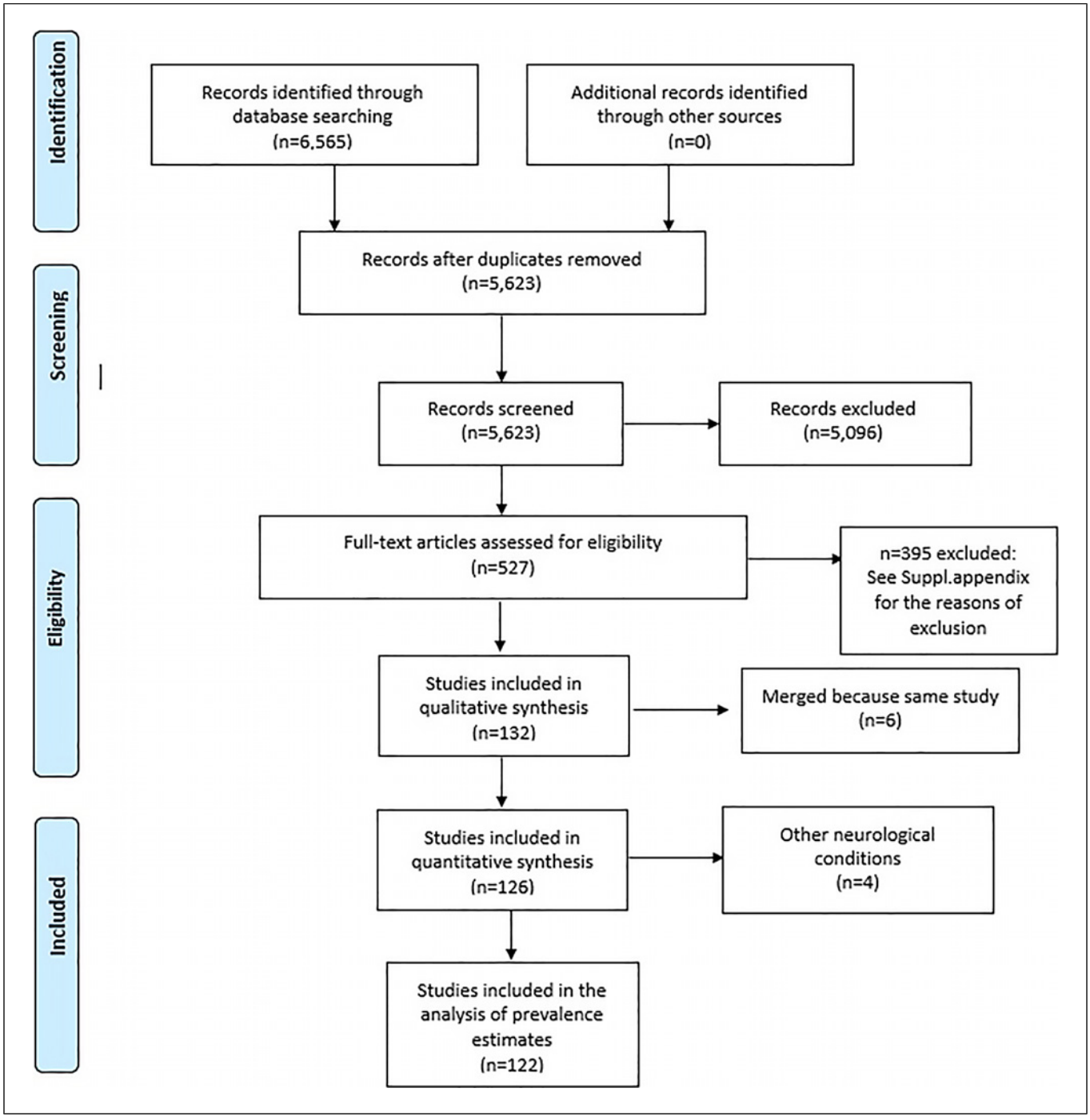


Fig. 1. Prisma study flowchart.

from the pre-specified periods, the data were entered at the closest time point (e.g., 4 months, approximated to 3 months). When only the mean/median duration of follow-up was reported, this was considered to be the time point. The neurological manifestations were classified under categories from the World Health Organisation's (WHO) Global COVID-19 Clinical Platform Case Report Form (CRF) for post-COVID-19 conditions (Post-COVID-19 CRF) [18].

The following manifestations were discussed and selected to be included: neuromuscular disorders, encephalopathy/altered

mental status/delirium, movement disorders, dysautonomia, cerebrovascular disorders, cognitive impairment, sleep disorders, seizures, syncope/transient loss of consciousness (TLOC), fatigue, gait disturbances, anosmia/hyposmia, and headache, according to the WHO Post-COVID-19 CRF definition [18]. Since subjects affected by anosmia were lumped together with those affected by ageusia in some studies, we only counted the number of subjects affected by anosmia in this review.

Study Risk of Bias Assessment

The quality of the included studies was independently assessed by the investigators with the Newcastle-Ottawa Scale (NOS) [19] for non-randomised studies. All raters were trained in advance in the use and administration of the NOS. Each study was rated on eight elements that were classified into three groups: the selection of the study groups, the comparability of the groups, and the assessment of exposure or the outcome of interest for case-control or cohort studies, respectively. The quality of the studies was then stratified based on the NOS score: very high risk of bias (0–3), high risk of bias (4–6), and low risk of bias (7–9).

Statistical Analysis

The statistical analysis was pre-planned. The primary outcome was the pooled prevalence (per 100 subjects) of each neurological manifestation at each follow-up period (3, 6, 9, and 12 months). A descriptive summary of the included studies is shown in Table 2 with details about study characteristics, as well as the number and characteristics of the enrolled subjects. The prevalence of neurological manifestations that occurred before, during, or after the acute phase of COVID-19 was calculated as the proportion of cases with each manifestation to the total number of subjects evaluated in each study at each time point.

Pooled prevalence estimates with 95% confidence intervals were calculated using the *metaprop* function in the software R (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria; URL: https://www.R-project.org/). Variability between studies and heterogeneity were evaluated using the between-study variance (τ^2, which is an estimate of the variance of the underlying distribution of the true prevalences across studies) and the I^2 statistic (I^2>50% indicates considerable heterogeneity), respectively. The p value of the Q-test for heterogeneity was also calculated ($p < 0.005$ indicates statistically significant heterogeneity). Given that substantial or considerable heterogeneity [20] was expected (I^2>50%), random effects models were used to obtain pooled prevalences, using the restricted maximum likelihood method (REML) and applying the double arcsine transformation to the observed prevalences. The meta-analysis was performed for each manifestation and for each follow-up period separately and only included studies that reported data for the corresponding manifestation at time points of the follow-up.

Pooled prevalences at each time point were also estimated in studies that only included hospitalised subjects and in studies that only included non-hospitalised subjects. Differences in the pooled prevalences between subgroups (hospitalised vs. non-hospitalised) were tested calculating the between subgroups heterogeneity Q-statistic and the relative p value ($p < 0.05$ indicates significant differences between subgroups). All analyses were performed using the SAS statistical package (version 9.4, SAS Institute, Cary, NC, USA) and the software R.

Role of the Funding Source

There was no funding source for this study. The study was conceived and supported by the "Global COVID-19 Neuro Research Coalition" in collaboration with the "Follow-up and long-term impact working group of the COVID-19 WHO Neuro-Forum" of the WHO Brain Health Unit, Department of Mental Health and Substance Use. However, the WHO had no role in study design, data collection, data analysis, data interpretation, or the writing of the report.

Results

Among 6,565 screened articles, 132 fulfilled the eligibility criteria, reporting on 126 unique studies (Fig. 1). Online supplementary Table 2 reports the reasons for exclusion during the full-text screening. No additional paper was manually identified from the reference list of the retrieved studies. The included papers are listed in the online supplementary Table 3. Forty-six countries from all continents except Antarctica were represented (Fig. 2 and online suppl. Table 4). Most of the reports came from Italy, the USA, Spain and the UK (online suppl. Table 4).

The total study population included 1,542,300 cases. Thirty-two studies included both cases (n = 1,499,263) and controls (n = 15,039,056), and 94 studies included cases only (n = 43,037). The number of included cases per study ranged from 5 to 735,870 [21]. Table 2 shows the characteristics of the included studies. The pooled mean age was 49.1 years (95% CI: 46.9–51.4); 825,127 (53.7%) were women and 711,650 (46.3%) men. In 5,523 cases, sex was either not reported or subjects did not identify with male or female sex. COVID-19 diagnosis was determined by swab polymerase chain reaction/antibody testing in 83 (65.9%) studies, by clinical diagnosis in three (2.4%) studies, and via multiple (mixed) methods in 22 studies (20.4%). The information about the percentage of patients with confirmed COVID-19 infection in each paper was available in 92 studies, of which 76 detected SARS-CoV-2 in 100% of the included subjects. The proportion of subjects who required hospitalisation was described in 82 studies (44.0%; 95% CI: 43.9–44.2%); 57 papers reported data about patients requiring ICU admission (4.3%; 95% CI: 4.2–4.4%); and 51 studies reported mortality for COVID-19 (3.2%; 95% CI: 2.9–3.5%) (Table 2).

The number of studies that provided information about the frequency and type of neurological manifestations varied between 15 (12%) and 78 (62%) for the different pre-specified time points. Most studies were observational (n = 124, 98.4%), with prospective (n = 48, 38.1%) or retrospective cohorts (n = 42, 33.3%) (Table 2).

Table 2. Characteristics of the studies included in the systematic review

Characteristics of the included studies (n = 126)	
Total number of included COVID-19 cases	1,542,300
Mean age (95% CI)	49.1 (46.9–51.4)
Sex, %	Female: 825,127 (53.5) Male: 711,650 (46.1) Other: 5,523 (0.4)
Countries represented in study population, n (%)	Multiple countries: 11 (8.7) Single country: 115 (91.3)
Study centres, n	Multicentric: 43 (34.1%) Monocentric: 83 (65.9%)
Average length of follow-up	Mean: 6.2 months (SD = 2.8 months)
Studies that evaluated at least one neurological manifestation at each pre-specified time point, n	Pre-acute: 33 (26.19%) Acute: 78 (61.90%) 3 months follow-up: 62 (49.21%) 6 months follow-up: 45 (35.71%) 9 months follow-up: 16 (12.70%) 12 months follow-up: 15 (11.90%)
Source of data	Registries: 10 (7.9%) Administrative databases: 25 (19.8%) Questionnaires: 60 (47.6%) More than one source: 31 (24.6%)
Study type	Observational: 124 (98.4%) Randomised: 0 (0%)
Study design	Case series (more than 5 cases): 9 (7.4%) Cross-sectional: 18 (14.3%) Case control: 9 (7.4%) Retrospective cohort: 42 (33.3%) Prospective cohort: 48 (38.1%)
Type of sampling	Random: 5 (4.0%) Quasi-random: 1 (0.8%) Consecutive: 60 (47.6%) Convenience: 34 (27.0%) Other: 15 (11.9%) Not reported: 11 (8.7%)
Outcome assessment	Face-to-face: 42 (33.3%) Mixed: 19 (15.1%) Postal: 8 (6.4%) Telephone: 44 (34.9%) Web survey: 1 (0.8%) Unknown: 12 (9.5%)
Newcastle-Ottawa Scale (NOS) quality assessment	Very high risk of bias (0–3 points): 19 (15.1%) High risk of bias (4–6 points): 80 (63.5%) Low risk of bias (7–9 points): 27 (21.4%)
Hospitalisation	Hospitalised: 54 (42.9%) Non-hospitalised: 24 (19.1%) Mixed: 28 (22.2%) Unknown: 20 (15.9%)
Mention of COVID-19 vaccination	Vaccination mentioned: 7 (5.6%) Vaccination not mentioned: 105 (83.3%) Unknown: 14 (11.1%)

Table 2 (continued)

COVID-19 variant assessed	Variant assessed: 50 (39.7%) Variant not assessed: 76 (60.3%)
COVID-19 severity evaluated	Severity evaluated: 59 (46.8%) Severity not evaluated: 49 (38.9%) Unknown: 18 (14.3%)
COVID-19 diagnosis confirmation (n = 92)	100% of subjects: 76 (82.6%) 99–80% of subjects: 5 (5.4%) 79–50% of subjects: 3 (3.3%) <50% of subjects: 8 (8.7%)

CI, confidence interval; SD, standard deviation.

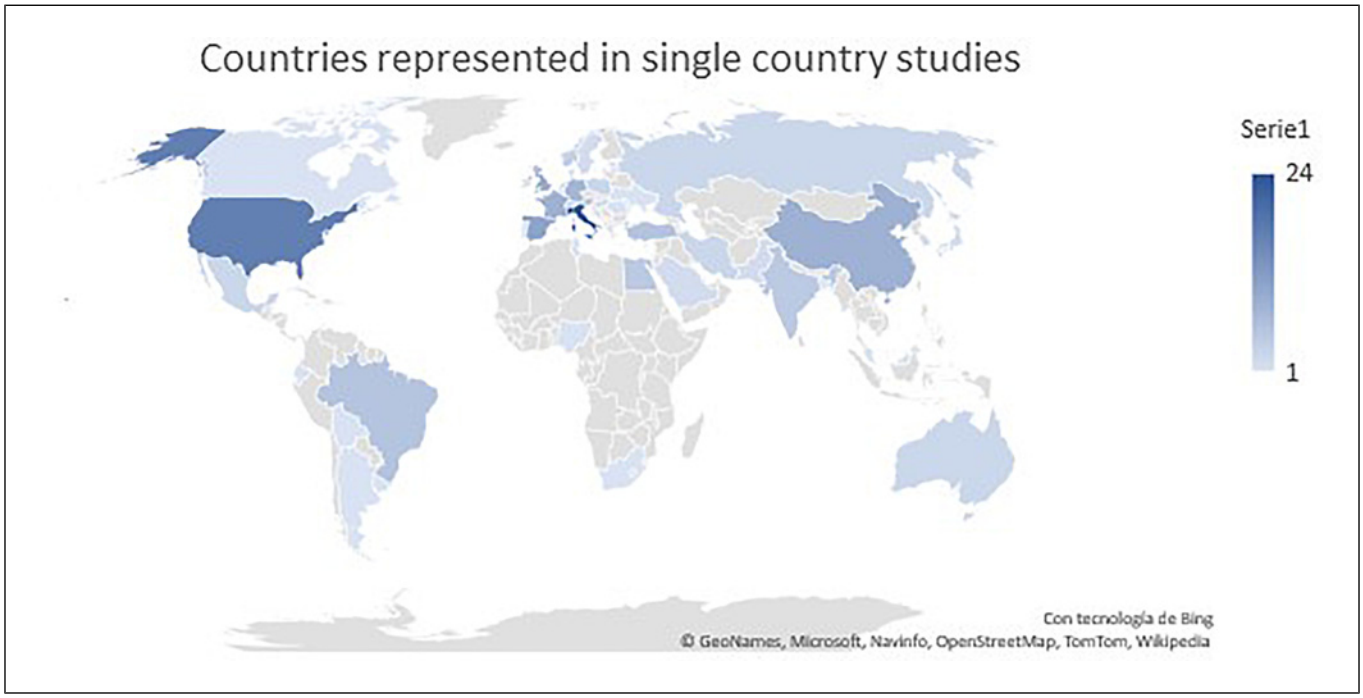
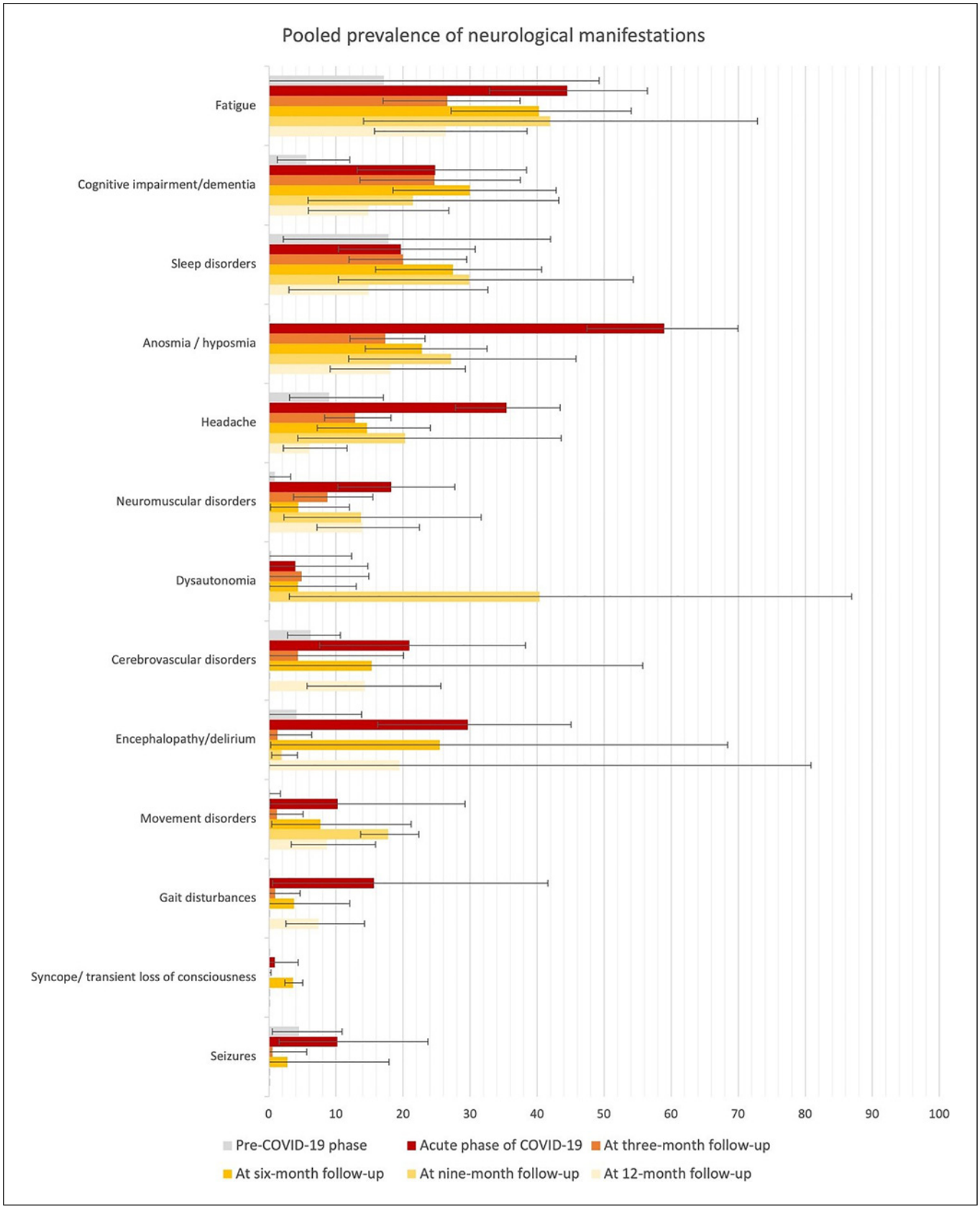


Fig. 2. Distribution of countries in the included studies.

Data were collected at a single centre in 83 (65.9%) and at multiple centres in 43 (34.1%) studies. Eleven (8.7%) studies spanned multiple countries. The most common sampling method was consecutive (n = 60, 47.6%). Outcomes were mostly evaluated by telephone (n = 44 studies, 34.9%) or in-person (n = 42, 33.3%).

From the 126 studies that we analysed, we extracted 13 neurological manifestations for which pooled prevalences and their 95% CI were calculated for at least one of the follow-up time points (Fig. 3, 4). Four studies only reported data about neurological conditions other than the 13 selected (vertigo/dizziness, tinnitus, dysphonia, primary CNS lymphoma, and brain tumor) and therefore were excluded [22–25]. The neurological conditions with reported prevalences higher than 20% during the acute phase of COVID-19 were anosmia/hyposmia (58.9; 95% CI: 47.4–70.0), fatigue (44.5; 95% CI: 32.9–56.5), headache (35.4; 95% CI: 27.8–43.4), encephalopathy (29.7; 95% CI: 16.2–45.1), cognitive impairment (24.8; 95% CI: 13.238.4) and cerebrovascular disease (21.0; 95% CI 7.6–38.2). Neurological disorders were also present in our pooled patient population before SARS-CoV-2 infection, with sleep disorders (17.8; 95% CI: 2.1–42.0) and fatigue (17.2; 0.1–49.3) being present in almost 20% of



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individuals who were assessed for pre-COVID-19 manifestations. At 3-month follow-up, the pooled prevalence of fatigue, cognitive impairment, and sleep disorders was 20% and above, and the prevalence of anosmia/hyposmia and headache was above 10%. For the subsequent time points, we observed different patterns. All five disorders showed a tendency towards persisting high prevalences at 6 and 9 months, although most prevalences were lower than in the acute phase. Cognitive impairment and sleep disorders were found at even higher prevalences at 6 months and sleep disorders in addition at 9 months than in the acute phase, but prevalences for all five conditions decreased at 12 months (fatigue 26.4, 95% CI: 17.0–37.5; anosmia/hyposmia 18.2, 95% CI: 9.1–29.3; sleep disorders 14.9, 95% CI 3.0–32.6; cognitive impairment 14.8, 95% CI: 5.9–26.8; and headache 6.07, 95% CI: 2.13–11.67) below those of the acute phase, although these conditions still occurred to a considerable extent in the patients studied and fatigue and cognitive decline remained above pre-COVID-19 levels.

Other disorders such as neuromuscular disorders, encephalopathy, cerebrovascular disorders, and seizures, which occurred with high prevalence during the acute phase of COVID-19, portrayed more fluctuating trajectories with wide confidence intervals at each follow-up time point (Fig. 3, 4). Complete information about the pooled prevalences over time for each of the neurological disorders is available in the online supplementary Tables 5–10. Overall, reported prevalences varied greatly across neurological disorders and time points, which needs to be taken into consideration when interpreting the results and their trends as depicted in Figures 3 and 4. In addition, variability/heterogeneity measures and the large confidence intervals indicate significant heterogeneity for each neurological manifestation at each follow-up (online suppl. Tables 5–10). Furthermore, we were unable to perform analyses according to age groups and sex, as disaggregated information was largely missing.

We conducted further analyses of hospitalised versus non-hospitalised people suffering from COVID-19 (online suppl. Table 11). Fifty-four studies reported on hospitalised individuals only, 24 on non-hospitalised individuals only, 28 included mixed populations, and in 20 studies, it was unknown whether subjects were hospitalised or not (Table 2). For our analysis, we referred to the 54 studies with hospitalised and 24 studies with non-hospitalised individuals, which included 131,520 and 8,702 individuals, respectively. Prevalences were significantly higher in non-hospitalised subjects for the following manifestations: sleep disorders in the pre-COVID-19 phase; headache, fatigue, anosmia/hyposmia, and sleep disorders in the acute phase of COVID-19; dysautonomia at 3-month follow-up; cognitive impairment at 6-month follow-up; neuromuscular disorders at 9-month follow-up; and anosmia/hyposmia at 12-month follow-up. Only the prevalence of sleep disorders at 9-month follow-up was higher in hospitalised subjects (online suppl. Table 11).

Discussion

Neurological manifestations are prevalent during the acute phase and contribute to the disability caused by SARS-CoV-2 infection [2–6]. For most conditions, our pooled prevalences during the acute phase were higher than those found by Misra et al. [7] in a systematic, comprehensive review of 350 articles, where the pooled prevalences of the most common acute neurological symptoms included fatigue (32%), myalgia (20%), taste impairment (21%), smell impairment (19%), and headache (13%), with stroke as the most common neurological disorder (2%; as opposed to neurological signs/symptoms). For this reason, we cannot exclude the possibility that follow-up studies were preferentially conducted in those settings with a higher prevalence of neurological manifestations during the acute phase and may therefore skew the perceived prevalence of post-COVID-19 neurological signs/symptoms/disorders in the general population. Nevertheless, the present study was not designed to depict the prevalence of neurological manifestations during the acute phase, but the post-acute phase.

This systematic review and meta-analysis provides data about the prevalence of neurological manifestations from the literature published during the first two and a half years of the pandemic. The best evidence on the prevalence of neurological signs/symptoms/disorders in COVID-19 survivors came from large studies [24] or registries [10], meta-analyses of general long-COVID-19 manifestations [11, 12], three neurology-specific meta-analyses with <15,000 COVID-19 cases [12–14], and meta-analyses of single neurological manifestations [26–29]. More than 1.5 million COVID-19 survivors

Fig. 3. Pooled prevalence of neurological manifestations, pre-COVID-19, during the acute phase of COVID-19, and at 3-, 6-, 9-, and 12-month follow-up. Pooled prevalences are reported as number of affected subjects/100 individuals with 95% confidence interval (bars).

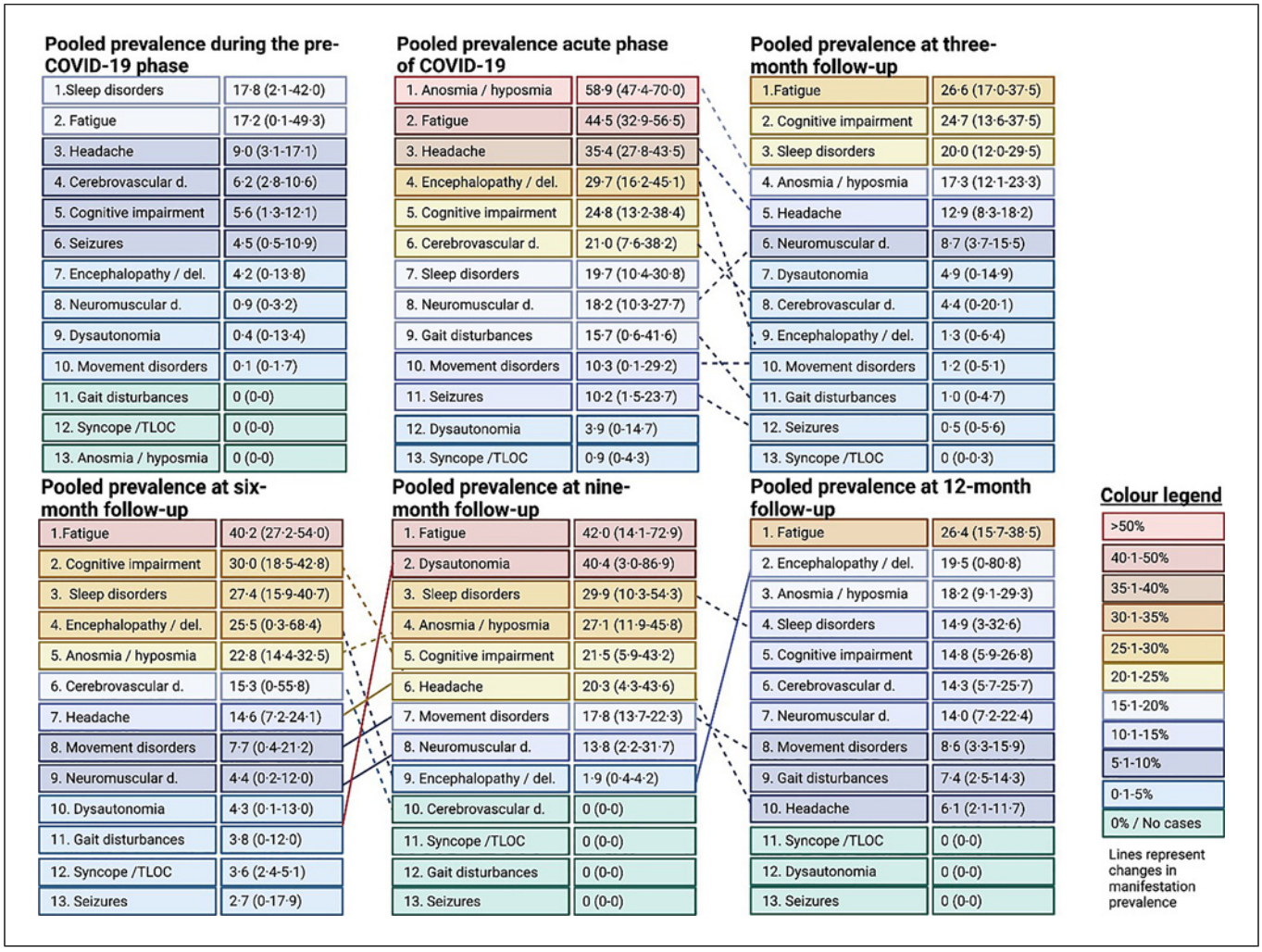

Fig. 4. Ranking of neurological manifestations over time, including pre-COVID-19, during the acute phase of COVID-19, and at 3-, 6-, 9-, and 12-month follow-up. Pooled prevalences are reported as number of affected subjects/100 individuals with 95% confidence interval.

from 46 different countries are represented in this review, and we have generated data about the trajectories of the neurological manifestations for up to 1 year after the acute phase of COVID-19.

Our data show that approximately one-third of COVID-19 survivors were affected by neurological signs/symptoms/disorders during the 12 months after the acute phase of COVID-19. Whether those prevalences are in excess of what is normally observed in the general population is not easy to ascertain as our five most prevalent neurological manifestations represent rather neurological symptoms than disorders which are normally the basis for epidemiological calculations such as the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), which represents the most comprehensive source of data on the global burden of neurological disorders. Van der Maaden et al. [30] in their study created random population-specific prevalence estimates tailored to the neurological signs/symptoms experienced by COVID-19 survivors at 3 months. Online supplementary Table 12 shows those values compared to our own results between 3-month and 12-month follow-up (minimum and maximum of our evaluations at 3, 6, 9, and 12 months are given), including fatigue, loss of smell, problems with memory, sleep problems, and headache, clearly demonstrating higher prevalences for post-COVID-19 neurological signs/symptoms from our study, apart from headaches [30]. This could be due to the difficulty in distinguishing between primary and secondary headaches in the general population; another

reason could be that headaches were underestimated in our population.

Overall, the most prevalent neurological signs/symptoms during the acute phase of COVID-19 and over the 1-year follow-up were cognitive impairment, sleep disorders, fatigue, anosmia/hyposmia, and headache. The prevalences of fatigue, anosmia/hyposmia and headache declined over time compared to those seen during the acute phase of COVID-19, although they remained high during follow-up. In contrast, the prevalences of sleep disorders and cognitive impairment increased further during the follow-up period beyond those observed during the acute phase of COVID-19. At 12 months, all five disorders returned to prevalences below those during the acute phase, although fatigue and cognitive decline remained above the prevalences calculated for the pre-COVID-19 phase.

The variable trajectories of these neurological manifestations could be caused by various reasons, such as new-onset neurological signs/symptoms arising during the follow-up period. Unfortunately, our study design did not allow us to differentiate between persistent neurological signs/symptoms from the acute phase of COVID-19 and new-onset neurological signs/symptoms that were not present during the acute phase of COVID-19. Alternatively, the differing trajectories could be related to the different pathophysiologies of the manifestations [7]. On the one hand, the neurological manifestations seen during the acute phase of COVID-19 may result from the virus, the acute immune response to the infection, or the prothrombotic state [30, 31]. On the other hand, manifestations observed after the acute phase may be due to virus persistence, chronic autoimmunity, or organ injury resulting from the acute phase [32–34], leading to persistent or new-onset manifestations. Other explanations may be the exacerbation of pre-COVID-19 morbidities (Fig. 3, 4) or underlying psychiatric conditions such as mood disorders [29]. However, one must also take into consideration that our review spans time periods with varying virus subtypes and data of different geographic origins due to the variability and heterogeneity of the included studies, resulting from different study designs, study populations, number of studies, and included individuals (Fig. 2; online suppl. Tables 4–10). Finally, during the follow-up period, non-hospitalised individuals seemed to be more affected by neurological disorders including dysautonomia, cognitive impairment, neuromuscular disorders, and anosmia/hyposmia. This could be due to the fact that these manifestations are not associated with the severity of the disease and that even patients with mild disease may present with them in the post-COVID-19 phase [35]. Also, a higher mortality rate in hospitalised patients and a lower likelihood of reporting signs/symptoms in the most severely ill patients could have contributed to the differences between the two subgroups.

In the year after our search, three large cohort studies on post-COVID-19 neurological disorders have been published. Talhari et al. [36] conducted an electronic survey in Brazil to evaluate acute and post-COVID symptoms, disease severity, demographics, and pre-existing diseases. Van der Maaden et al. [30] performed a prospective study to assess symptoms after SARS-CoV-2 infection compared to test-negative and population controls, in the context of the Dutch prospective Long COVID Study. The third study enrolled patients in the French ComPaRe Long COVID prospective e-cohort, an ongoing nationwide e-cohort of COVID-19-positive patients reporting symptoms persisting for at least 2 months after infection [37]. Talhari et al. [36] and van der Maaden et al. [30] followed 6,958 and 9,166 patients, respectively, for 3 months, while Tran et al. [37] followed 968 patients for up to 1 year. Fatigue and cognitive impairment were frequently reported in all three studies, as well as headache, anosmia/hyposomia, and sleep disorders in individual studies. The results of these most recent studies support the findings of our systematic review and meta-analysis, showing that some neurological manifestations are among the most prevalent signs/symptoms of the post-COVID-19 condition. For exact prevalences of the three studies and comparison with our own values, refer to online supplementary Table 13, in which the prevalences of the five most frequent neurological manifestations have been listed. Our calculated prevalences were in a similar range to those of Talhari et al. [36] and van der Maaden et al. [30] at 3 months but below most of the prevalence estimates of Tran et al. [37] at 2 and 12 months, possibly because the Tran et al. [37] study selected only subjects with neurological manifestations present for at least 2 months for follow-up and because the same subjects were followed up for a longer period, whereas in our study the evaluation was cross-sectional at each time point.

Limitations

The findings of this review should be interpreted in the context of its limitations. Our systematic review/metanalysis represents a cross-sectional, non-longitudinal approach to each of the six analysed time points (pre-COVID-19, acute phase of COVID-19, 3-, 6-, 9-, and 12-month follow-up),

which means that we cannot comment on the extent to which pre-COVID-19 neurological morbidity influenced neurological signs or symptoms during the acute phase of COVID-19 and the follow-up time points. Based on the same reasons, we could not differentiate between persistence and the new onset of neurological signs/symptoms after the acute phase of COVID-19. Individuals were not followed up over time as they would have been in longitudinal studies; therefore, the various time points in our study cannot be connected, and no comment can be made on individual patient trajectories over time. Not all neurological manifestations were evaluated or reported systematically, and the number of studies addressing each manifestation varied significantly over time.

Overall, studies tended to focus on more frequently reported neurological signs/symptoms such as fatigue, anosmia/hyposmia, sleep disorders, cognitive impairment, and headache, whereas there were few studies on neurological manifestations such as movement disorders, syncope, and epilepsy. It would be important to also collect data on rarer neurological manifestations in the post-COVID-19 period, which may require a multicentre study design.

The lack of a control group, with people affected by other non-COVID-19 respiratory diseases, makes it difficult to interpret the specific contribution of COVID-19 to the prevalence of acute and chronic neurological signs/symptoms compared to those in the context of generic post-infectious illness. Only a handful of controlled studies [38–41] evaluated the overall excess incidence or prevalence attributable to COVID-19 compared to the natural trajectory of recovery from a serious viral illness. In one such study, Taquet et al. [38] evaluated an absolute risk increase of any long-COVID-19 feature of 16.6% compared to influenza. The 6-month risk was significantly higher for anxiety disorders, insomnia, cognitive deficit, epilepsy or seizures, and ischaemic strokes [38].

We also found notable variability and heterogeneity among the included studies due to different case definitions, diagnostic criteria, included disorders, sample sizes, study populations, follow-up periods, and methods of data ascertainment (online suppl. Tables 5–10). The great majority (n = 99, 78.6%) of the included studies had very high or high risk of bias. Many studies were focused on specific manifestations, and others only selectively reported data, possibly leading to biased results. This may be the reason why the prevalence of some manifestations, such as encephalopathy or cerebrovascular accidents, seems to exceed expected rates in some cases [27]. In addition, in these studies, confidence intervals were larger, signalling that the true prevalence of the manifestation in the population might be different than the observed point estimate.

Furthermore, the ascertainment of many disorders was based on different modalities, either subjective (self-report) or objective, thus limiting their comparability. Often, data were incomplete within single studies; disease determinants such as age, gender, pre-existing neurological disorders, and other co-morbidities as well as required hospitalisation were absent at the disaggregated data level, and therefore, these subgroup analyses could not be performed within the analysis of our study. Finally, studies did not distinguish between long-COVID-19 survivors from different waves of infection, so we could not separate the effect of the first, more severe, wave of SARS-CoV-2 infection from that of the other waves.

Conclusion

Despite the above limitations, the results from our study appear to be in line with recent large-scale studies with comparable study design; neurological manifestations seem to be highly prevalent after the acute phase of COVID-19. The neurological disorders with the highest overall prevalences were fatigue, cognitive impairment, sleep disorders, anosmia/hyposmia, and headache. The prevalence of sleep disorders and cognitive impairment even increased after the acute phase, while other neurological manifestations tended to decrease over time. In our study, prevalences appeared to be lowest at the end of the data collection period, suggesting that neurological manifestations in the early post-COVID-19 phase may be long-lasting but not permanent. However, this needs to be interpreted in light of fewer studies and, hence, fewer included individuals at the 12-month follow-up time point. More robust data at later follow-up time points are needed to elucidate the long-term trajectory of neurological disorders after the acute phase of COVID-19.

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Statement of Ethics

This paper is a systematic review and meta-analysis; for this reason, we did not enrol patients but used data from already published papers.

Conflict of Interest Statement

David García-Azorín received honoraria for lectures/presentations from AbbVie/Allergan, Eli Lilly, Teva, Lundbeck, and Novartis, as well as from the World Health Organization as a subject matter expert. He participated in clinical trials as the principal investigator for Pfizer, BioHaven, and Lundbeck and is the junior editor of The Journal of Headache and Pain. Jennifer A. Frontera received funding from the NIH for COVID-19-related research. Aynur Özge received honoraria for lectures/presentations from AbbVie/Allergan, Eli Lilly, Teva, Abdi İbrahim, İlko, Nestle, and Novartis. She is also a board member of the International Headache Society and the current president of the Global Migraine and Pain Society. She is also associate editor of Frontiers in Neurology Journal and serves as a reviewer of several journals including Headache, Cephalalgia, and The Journal of Headache and Pain. Andrea S. Winkler reports funding by the School of Medicine, Technical University of Munich, Grant Number H.40001.1.7-08 in support of the Global COVID-19 Neuro Research Coalition. All other authors have no conflicts of interest to declare.

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Author Contributions

Concept, design, and critical revision of the manuscript for important intellectual content: Giorgia Giussani, Erica Westenberg, David Garcia-Azorin, Maurizio Leone, and Andrea Sylvia Winkler. Paper revision, data entry, and review of the manuscript: all authors. Drafting of the manuscript: Giorgia Giussani, Erica Westenberg, and David Garcia-Azorin. Data management: Giorgia Giussani and Maurizio Leone. Statistical analysis: Elisa Bianchi. Supervision: Giorgia Giussani, Maurizio Leone, and Andrea Sylvia Winkler.

Data Availability Statement

Data will be available upon request to the authors.

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