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SYSTEMATIC REVIEW

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A systematic review to find link between past psychiatric history and development of long covid

Charlotte Bessaguet^{1*}, Anthony Bonilla^{1*}, Clément Polin^{1,2}, Aurélie Lacroix^{2,3*} and Leslie Cartz-Piver^{1,3*}

Abstract

Background Covid-19 is a pandemic acute infectious disease that emerged in 2019. It is estimated that 10–20% will develop persistent symptoms, known as long Covid or post-Covid syndrome. The risk factors for the development of this syndrome are still being studied. Psychosocial factors are known to increase the duration and severity of respiratory infections.

Aims (i) to review current knowledge of the link between past psychiatric history and the development of long Covid; (ii) to obtain information on the psychological experience of the initial infection; (iii) to establish a link between the presence of psychiatric symptoms during the acute phase and the development of long Covid.

Method We conducted a systematic review according to PRISMA standards using the Pubmed, Science Direct and Scopus databases. We included observational studies of adult subjects with long Covid whose psychiatric and/or addictive histories were searched.

Results A total of 36 articles were included in our review. Depression and anxiety appear to be risk factors for the development of long Covid. There is no consensus on the contribution of smoking to the onset of the syndrome. The negative psychological experience of the acute infection favours the persistence of symptoms. Psychological symptoms during the acute phase, studied in only one of our articles, seem to contribute to the persistence of concentration and attention problems.

Conclusion Psychological comorbidities pre-existing COVID-19 infection, in particular depression and anxiety, as well as a poor psychological experience of the acute phase, may favour the development of long Covid.

Trial registration number PROSPERO registration number CRD42023391720.

Keywords Past psychiatric history, Past addiction history, Risk factors, Long covid

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Background

COVID-19 is an acute respiratory infection caused by a coronavirus SARS-CoV-2. Since its appearance in Wuhan, China in 2019, the disease has spread worldwide causing approximately 750 million confirmed cases [1]. Most people recover from acute COVID within 2–3 weeks [2], but in 10–20% cases, symptoms are prolonged [3].

In 2021, the World Health Organization (WHO) defined this prolonged post-infectious state using the term "long Covid" or "post-Covid syndrome", characterized by persistent symptoms generally appearing 3 months after the onset of probable or confirmed SARS-Cov-2 infection and lasting at least 2 months, which cannot be explained by another diagnosis. The notion of "post-Covid condition" was introduced into the International Classification of Diseases (ICD-10) with code U09.9 [3]. In France, the Haute Autorité de Santé (HAS) defines the post-Covid condition as "an initial symptomatic episode of confirmed or probable COVID-19, with the persistence of at least one of the initial symptoms beyond 4 weeks following the onset of the acute phase of the disease and not explained by another diagnosis" [4].

This emerging post-Covid condition is still poorly defined. Its symptoms are unspecific, diverse and multi-systemic (over 200 symptoms have been identified). The most frequent symptoms are dyspnea, cough, chest pain, joint and muscle pain, smell and taste disorders, fatigue, insomnia, anxiety, depression and cognitive complaints [5–10].

Persistent symptoms can have a negative impact on quality of life, including difficulties in daily activities, reduced physical activity and difficulties returning to work [11–13]. A French cohort study by Ghosn et al. [14] showed that a third of Covid long patients had not returned to work 6 months after the initial infection. Persistent symptoms can also lead to mental disorders such as anxiety, depression and sleep disorders [15].

Numerous studies have identified several risk factors, such as initial severity of infection (hospitalization and/or oxygen therapy) [16–21], female gender [16–18, 20], advanced age [17, 18], obesity [19] and diabetes [17, 19]. A risk of suicide in individuals with prior mental disorders was found [22], with more severe injuries such as bone fractures and fewer inherited injuries such as overmedication [23], showing the vulnerability of this population to Covid pandemic. It is well established that psychosocial factors can influence diseases such as infections, cancers and autoimmune diseases via the immune system [21]. In the case of respiratory infections, psychological stressors have been shown to increase symptom severity and duration [24, 25]. In the case of COVID-19, little attention has been paid to potential contribution

of psychiatric disorders to the onset of this syndrome [26–29].

The Main objective of this systematic review of the literature, is to collect current knowledge of links between past psychiatric history and the development of a long Covid. Secondary objectives are to obtain information on the psychological experience of the acute infection, and to establish a link between the presence of psychiatric symptoms during the acute phase and the development of a post-Covid syndrome.

Methods

Search

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [30]. An extensive bibliographic search was carried out using the *Pubmed*, *Science Direct* and *Scopus* databases. Human Ethics and Consent to Participate declarations were not applicable. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42023391720) [31]. There was no Funding relative to this study.

Keywords or Mesh Terms including "long covid" were used to target this particular syndrome. The Boolean operator "AND" was added to link search terms (on title, abstract or Mesh Terms) concerning psychiatric and/or addictive history, then again for links with risk factors. Synonyms or equivalent terms were added using the Boolean operator "OR". The search equations are detailed in Fig. 1.

This search was carried out up to March 1, 2023.

The review was based on a research question developed according to the PICO scheme, namely: Population (P): subjects ≥ 18 years old with long Covid syndrome, Intervention (I): presence of psychiatric and addiction history, Comparison (C): absence of psychiatric and addiction history, and Outcome (O) Links between psychiatric history and development of long Covid.

Eligibility criteria

Studies of subjects with post-Covid syndrome were eligible for inclusion in this systematic review. Long Covid was defined as a persistent symptomatology after an acute Covid infection, and for which no other diagnosis can explain the disorders presented. Studies whose participants were in the acute phase during the study were not included. To be eligible, studies also had to investigate past psychiatric and/or addictive histories. Studies selected by our search equation that did not meet the primary objective but did meet one of the secondary objectives were also included. Articles published from 2020 onwards, written in English or French, were included in the search. This included cross-sectional studies,

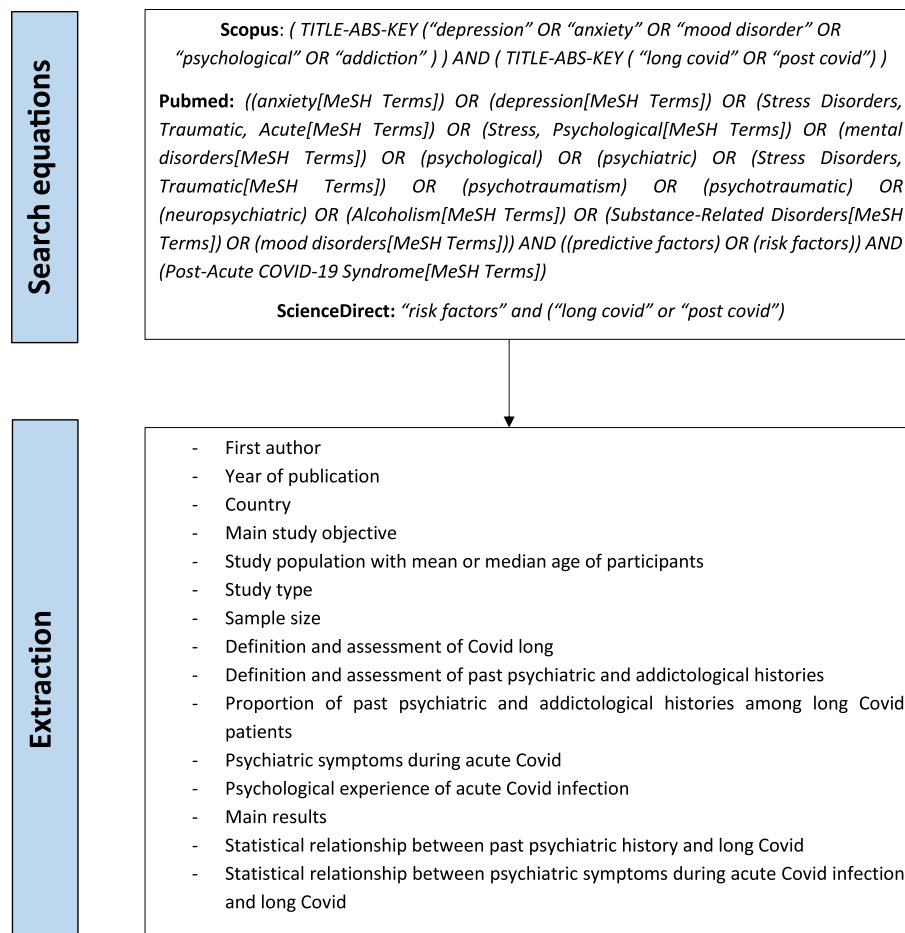


Fig. 1 Scheme of the method

prospective or retrospective cohort studies, case–control studies and descriptive studies.

Literature reviews, review articles, systematic reviews, meta-analyses, case studies, good practice guidelines, legal texts and book chapters were excluded from the review. Studies involving minors (<18 years) were also excluded.

Study selection

All articles identified by the search equations were saved and imported via the bibliographic software Zotero [32], then the Rayyan application [33] was used to facilitate study selection and identification. Duplicates were removed. Two investigators (AB and CB) then double-blinded the titles and abstracts of the articles according to inclusion and non-inclusion criteria. After this initial screening, all remaining articles were searched and read to assess their eligibility for a second selection. Meetings were held between the investigators to reach a consensus on the inclusion or exclusion of articles in case of conflict. Selected publications were included in the literature review.

Quality assessment

The Newcastle–Ottawa Scale (NOS) [34] for non-randomized studies was used to assess the quality of each study. This scale comprises three main components: 1/selection of the study sample (four questions), 2/comparability of subjects in the different outcome groups (one question), 3/exposure, results and statistical tests (two or three questions, depending on the type of study). The overall score ranged from 0 to 10 for cross-sectional studies, and from 0 to 9 for longitudinal and case–control studies. The scores obtained were classified into four groups: articles with an overall score of less than 4, 5 to 6, 7 to 8 and 9 to 10 were considered to be of poor, average, good and very good quality respectively.

The quality assessment of the included articles was carried out in double-blind. Meetings were organized between the investigators to reach consensus in the event of conflict.

Data extraction and synthesis

The information extracted are detailed in Fig. 2. Because of diversity of included studies and quantitative results,

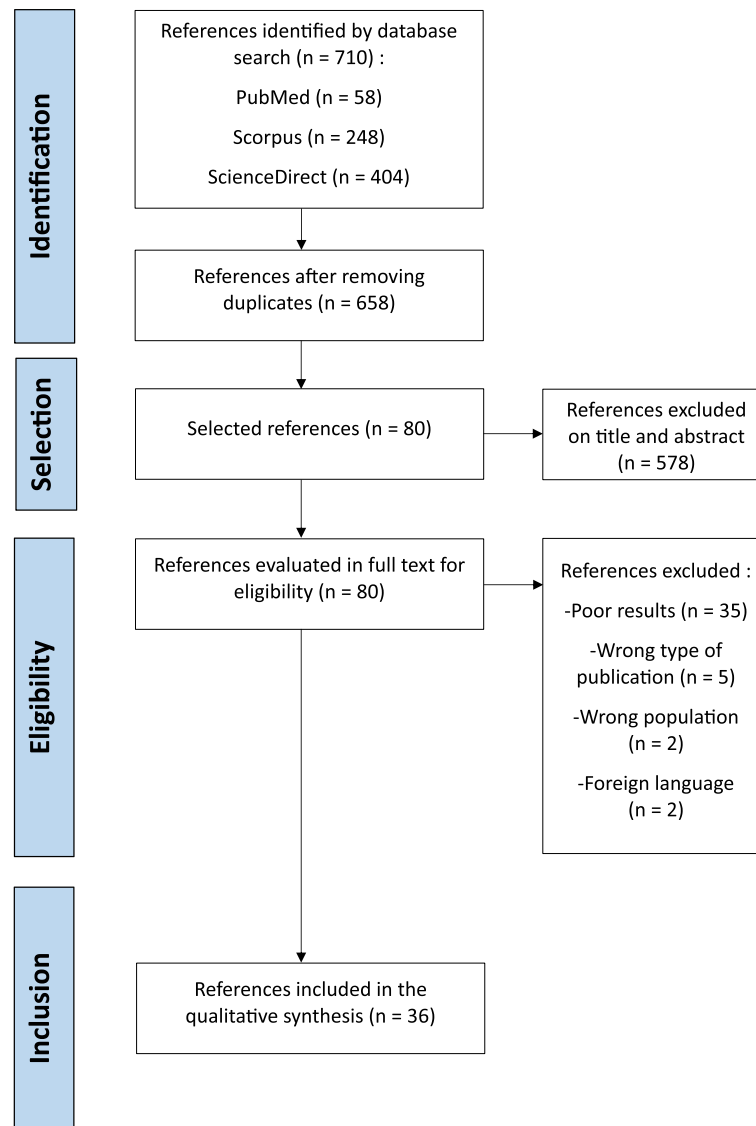


Fig. 2 Flow chart according to PRISMA

a narrative synthesis of the data was produced. Where percentages were not presented in the articles, calculation was based on available data. No additional statistical analysis or meta-analysis was performed because of the diversity of the articles and the disparity in psychiatric history subgroups. Studies with NOS criteria below 4 were not included in the qualitative synthesis.

Results

A total of 710 articles were identified and extracted using a combined search of the various databases. Of the initial 710 articles, 658 remained after removing duplicates. After an initial selection based on titles and abstracts, 578 articles were excluded. 80 articles were retained and evaluated in their entirety. 35 articles had a wrong outcome, i.e. there was no information about psychiatric and/or

addiction history among long Covid subjects. A wrong population with study of acute Covid infection only was present in 2 articles. 2 articles were excluded because they were written in a language other than French or English. Finally, the wrong types of publication, i.e. dealing with research protocols and meta-analyses, numbering 5, were excluded. In the end, 36 articles were included in this review (cf Fig. 2).

Characteristics of included studies (cf Table 1)

Of the studies included in the review, 3 were case-control studies [56, 63, 65], 13 were prospective cohorts [36–38, 43, 45, 47, 49, 51, 53–55, 60, 68], 4 were retrospective cohorts [35, 40, 69, 71] and 16 were cross-sectional studies [39, 41, 42, 44, 46, 48, 50, 52, 57, 58, 61, 62, 64, 66, 67, 70]. The studies were published between 2020 and 2023.

Table 1 Characteristics of included studies in the review

N°	Author(s) and year	Country	Main aim of the study	Study population	Study design	Sample size (% female)	Age (mean or median)
1	Subramanian et al., 2022 [35]	United Kingdom	To investigate a comprehensive range of symptoms previously reported to be associated with long COVID by epidemiological studies, patients and clinicians. To assess their association with confirmed SARS-CoV-2 infection at least 12 weeks after infection in non-hospitalized adults, compared to a propensity score-matched cohort of patients with no recorded evidence of SARS-CoV-2 infection. To assess associations between demographic and clinical risk factors, including comorbidities, with the development of long COVID and characterized dominant symptom clusters	Adults with confirmed SARS-CoV-2 with symptoms persisting beyond 12 weeks, from a UK-based primary care database, propensity score-matched adults with no recorded evidence of SARS-CoV-2 infection	Retrospective cohort study	N = 2 430 729 (55.3%) Sample size for analysis of risk factors for long covid: N = 384 137 (55.3%)	43.8 ± 16.9 (mean)
2	Wang and al., 2022 [36]	USA	To determine whether high levels of psychological distress before SARS-CoV-2 infection, characterized by depression, anxiety, worry, perceived stress, and loneliness, are prospectively associated with increased risk of developing post-COVID-19 conditions	Participants of 3 ongoing longitudinal studies (Nurses' Health Study II (NHSII), Nurses' Health Study 3 (NHS3), and the Growing Up Today Study (GUTS)) with an antecedent of positive SARS-CoV-2	Prospective cohort study	N = 3 193 (96.4%)	Cases (post-Covid pain): 43 (σ 15.85) Controls (absence of pain): 45.71 (σ 13.89) (mean)
3	Grisanti and al., 2022 [37]	Italy	To characterize a population of patients with prior COVID-19 infection who showed signs and symptoms consistent with neurological long-COVID. Further, to analyze the patterns of symptoms persisting three months after the end of the acute phase of COVID-19 infection and discuss the presence of subtypes of neurological long-COVID, and their potential risk factors	Long Covid subjects with neurological symptoms	Prospective cohort study	N = 109 (50%)	55.17 (18-80) (mean)
4	Garjani and al., 2022 [38]	United Kingdom	To understand the course of recovery from coronavirus disease 2019 (COVID-19) among patients with multiple sclerosis (MS) and to determine its predictors, including patients' pre-COVID-19 physical and mental health status	Patients with multiple sclerosis who reported Covid-19 infection	Prospective cohort study	N = 571 (77.2%)	Not calculated in the overall study population
5	Craparo and al., 2022 [39]	Italy	To identify clusters of long COVID-19 symptoms using latent class analysis and investigate the psychological factors involved in the onset of this syndrome	Italian individuals with an official diagnosis of COVID-19 who recovered from the disease	Cross-sectional	N = 506 (86%)	Not calculated in the overall study population
6	Tene and al., 2022 [40]	Israel	To examine the prevalence of long COVID in a large population-based cohort and to characterize its demographics and clinical risk factors	Subjects who had a covid infection objectified by a RT-PCR test among members of a large health provider in Israel	Historical cohort	N = 180 759 (49.6%)	32.9 (σ 19) (mean)
7	De Oliveira and al., 2022 [41]	Brazil	To describe the prevalence and type of consequences of COVID-19 after acute recovery, evaluate the quality of life, and identify potential risk factors associated with long COVID	Surviving patients with Covid-19 discharged from Eduardo de Menezes Hospital	Cross sectionnal	N = 439 (49.7%)	58 (47-67) (median)

Table 1 (continued)

N°	Author(s) and year	Country	Main aim of the study	Study population	Study design	Sample size (% female)	Age (mean or median)
8	Ohira and al., 2022 [42]	Japan	To examine the clinical characteristics of patients with long COVID in Japan	Long Covid subjects visiting a clinic (Department of General Internal Medicine of the National Center of Neurology and Psychiatry) in Japan	Cross sectional	N=91 (56.7%)	39.8 (σ 14.7) (mean)
9	Bai and al., 2022 [43]	Italy	To investigate the incidence of physical and/or psychological symptoms characterising the "long COVID" syndrome in female gender and to study the possible predictors of long COVID	Adults hospitalized for a SARS-CoV-2 infection who were evaluated at the post-COVID outpatient clinic	Prospective cohort	N=377 (36.3%)	57 (49–68) (median)
10	Daitch and al., 2022 [44]	Israel, Switzerland, Spain, and Italy	To describe the prevalence of long-COVID symptoms among older adults and to explore independent risk factors for two of the most common long-COVID symptoms: fatigue and dyspnea	Adults with a polymerase chain reaction-proved COVID-19 diagnosis at least 30 days before the clinic visit	Cross sectional	N=2 333 (49.2%)	51.25 (σ 16.39) (mean)
11	Afroze and al., 2022 [45]	Bangladesh	To assess the prevalence, incidence rate, evolution over time, and risk factors of post-covid-19 syndrome (PCS) among hospitalized (HS) and non-hospitalized (NHS) COVID-19 survivors	Adults with RT-PCR-confirmed COVID-19 and sought care from the study hospitals with or without the requirement for hospitalization, and showed significant improvement of symptoms for three consecutive days with concomitant hospital discharge	Prospective cohort study	N=362 (38%)	50 (38–60) (median)
12	Vásconez-González and al., 2023 [46]	Ecuador	To describe persisting symptoms after COVID-19 infection in pregnant and non-pregnant women in Ecuador	Pregnant and non-pregnant women in Ecuador with an history of Covid-19 infection	Cross sectional	N=457 (100%)	Not calculated
13	Frontera and al., 2022 [47]	USA	To evaluate the impact of four categories of predictors on 6- and 12-month outcome metrics including: demographics, pre-COVID-19 comorbidities, index COVID-19 hospitalization metrics, and life stressors within the month prior to interview	Patients hospitalized with acute Covid infection 6 and 12 months before follow-up interview	Prospective cohort	At 6 months follow up: N=382 (35%) At 12 months follow up: N=242 (36%)	At 6 months follow up: 69 (57–78) At 12 months follow up: 65 (53–73) (median)
14	Shukla and al., 2023 [48]	India	To assess the nature and prevalence of medical sequelae following COVID-19 infection, and risk factors, if any	Health care workers between 12 and 52 weeks post discharge after COVID-19 infection	Cross sectional	N=679 (50.81%)	31.49 ± 9.54 (mean)
15	Jacobs and al., 2023 [49]	USA	To ascertain which pre-existing conditions engendered a greater risk for the development of post-acute sequelae of covid (PASC) after SARS-CoV-2 infection	Arizona residents with an history of acute Covid infection	Prospective cohort	N=1 224 (45.6% in PACS+ and 54.4% in PACS -)	PACS -: 47 (33–60) PACS +: 49 (36–60) (median)
16	Knight and al., 2022 [50]	USA	To assess, characterize, and describe the prevalence and predicting factors of patient-reported severe coronavirus disease 2019 (COVID-19) infection and post-acute sequelae of COVID-19 (PASC)	Adults with an history of acute Covid infection who received care in the COVID-19 virtual clinic	Cross sectional	N=437 (60.2%)	54 (18–99) (median)

Table 1 (continued)

N°	Author(s) and year	Country	Main aim of the study	Study population	Study design	Sample size (% female)	Age (mean or median)
17	Sansone and al., 2022 [51]	Italy	To investigate the persistence of symptoms 15 months since COVID-19 diagnosis in patients referring to the post-COVID-19 clinic in Trieste (north-eastern Italy)	Long covid subjects attending the Long-COVID-19 outpatient clinic of Trieste	Prospective cohort	N=247 (64.4%)	48.1 (σ 10.5) (mean)
18	Yavuz and al., 2022 [52]	Turkey	To reveal post-COVID-19 neurological symptoms and risk factors for their development	Adults applied to four local Neurology Outpatient Clinics (two centers at city of Ankara, one each center at the city of Yozgat and Tokat) at least four weeks after contracting COVID-19 infection (confirmed by a laboratory test)	Cross sectional	N=400 (61%)	39.9 (σ 13.7) (mean)
19	Gutiérrez-Canales and al., 2022 [53]	Mexico	To identify sequelae and persistent symptoms, as well as their influence on quality of life, in outpatients who had recovered from COVID-19	Adults unvaccinated against SARS-CoV-2 at the time of infection, who had recovered from COVID-19 (2 to 12 months after the onset of symptoms)	Prospective cohort	N=206 (62.6%)	28 (22–45.5) (median)
20	Hastie and al., 2022 [54]	Scotland	To determine the frequency, nature, determinants and impact of long-COVID in the general population	Adults in Scotland with a positive PCR test for SARS-CoV-2 with a comparison group who had had a negative test but never had a positive test	Prospective cohort	N=96 238 (39%)	45 (median)
21	Fleischer and al., 2022 [55]	Germany	To validate subjective neurological complaints in patients with post-COVID-19 by applying a comprehensive neuropsychiatric diagnostic workup	Subjects fulfilling the WHO Delphi consensus criteria for post-COVID-19 syndrome	Prospective cohort	N=171 (66.7%)	45.2 ± 12.7 (mean)
22	Margalit and al., 2022 [56]	Israel	To assess risk factors for long-COVID fatigue and explored its possible pathophysiology	Adults who recovered from COVID-19 (had to be at least 2 months following a PCR-proven diagnosis of COVID-19)	Case–Control	N=141 (59%)	47 (σ 13) (mean)
23	Gasnier and al., 2022 [57]	France	To investigate the association between long COVID, psychiatric symptoms and psychiatric disorders	Subjects admitted in intensive care unit during acute phase of Covid-19 and/or reporting long COVID complaints	Cross sectional	N=177 (unspecified)	Not calculated in the overall study population
24	Loosen and al., 2022 [58]	Germany	To study the prevalence of Long COVID Syndrome (LCS) in Germany and to identify clinical factors associated with its development	Patients with a confirmed diagnosis of COVID-19 (ICD-10: U07.1) from one of 1056 GP practices that routinely send data to the Disease Analyzer database	Cross sectional	N=50 402 (54.5%)	48.8 (σ 19.3) (mean)
25	Buonsenso and al., 2022 [59]	Italy	To evaluate the sequelae of COVID-19 in a population of workers who tested positive for COVID-19, with a follow-up within one year of the acute illness, and to analyse the possible association between COVID-19 sequelae and changes in the workers occupational status	Adult members of the households of children diagnosed with SARS-CoV-2 infection (using RT-PCR) at the Department of Women and Child Health of the Fondazione Policlinico Universitario A. Gemelli IRCCS of Rome	Retrospective cohort	N=155 (50.3%)	46.48 (σ 7.302) (mean)

Table 1 (continued)

N°	Author(s) and year	Country	Main aim of the study	Study population	Study design	Sample size (% female)	Age (mean or median)
26	Lhuillier and al., 2022 [60]	USA	To examine physical and psychiatric antecedents associated with COVID-19 illness severity and post-acute COVID-19 sequelae presence among individuals who endorsed any COVID-19 infection	People who participated in the rescue and recovery efforts on 9/11 for the World Trade Center with a positive test result for COVID-19	Prospective cohort	N= 1280 (8.6%)	56.9 (σ 7.37) (mean)
27	Tleyjeh and al., 2022 [61]	Saudi Arabia	To determine the prevalence of COVID-19 associated symptoms 4 weeks or more after the onset of the disease and identify predictors associated with delayed return to baseline health state among these patients	Adults confirmed to have COVID-19 at least 4 weeks prior to the start of the survey	Cross sectional	N=5946 (35.6%)	Not calculated
28	Kidwai and al., 2022 [62]	Pakistan	To determine the prevalence of post-COVID syndrome in a cohort of faculty working in Fazaia Ruth Pfau Medical College (FRPMC), Karachi, Pakistan, and their family members	Faculty members of Fazaia Ruth Pfau Medical College (FRPMC) and their family, who suffered from COVID infection and who tested positive by polymerase chain reaction (PCR) test	Cross sectional	N= 84 (48.81%)	47.15 ± 14.81 (mean)
29	Magdy and al., 2021 [63]	Egypt	To assess risk factors for persistent neuropathic pain in subjects recovered from coronavirus disease 2019 (COVID-19) and to study the serum level of neurofilament light chain (NFL) in those patients	Subjects with post-COVID-19 pain and age and sex-matched healthcare workers who recovered from COVID-19 without pain	Case-control	N=90 (65.5%)	Cases (post-Covid pain): 43 (σ 15.85) Controls (absence of pain): 45.71 (σ 13.89) (mean)
30	Abdelhafiz and al., 2022 [64]	Egypt	To evaluate the prevalence of post-COVID-19 symptoms among Egyptian patients and detecting the factors associated with the presence of these symptoms	Egyptian subjects who had history of COVID-19 disease	Cross sectional	N= 396 (78.54%)	41.402 ± 11.151 (mean)
31	Ghoshal and al., 2021 [65]	India and Bangladesh	To study the frequency and spectrum of post-infection-FGIDs among COVID-19 and historical healthy controls and the risk factors for its development	Adults with an history of acute Covid infection, compared with a cohort of healthy subjects published earlier	Case-control	N= 280 (72.9%)	39.5 ± 15.4 (median)
32	Peter and al., 2022 [66]	Germany	To describe symptoms and symptom clusters of post-covid syndrome six to 12 months after acute infection, describe risk factors, and examine the association of symptom clusters with general health and working capacity	Adults aged 18–65 years with confirmed SARS-CoV-2 infection between October 2020 and March 2021 notified to health authorities in four geographically defined regions in southern Germany	Cross sectional	N= 11 710 (58.8%)	44.1 (σ 13.7) (mean)
33	Alkwai and al., 2022 [67]	Saudi Arabia	To describe and characterise the prevalence of persistent COVID-19 symptoms beyond three months and to evaluate the risk factors for the delayed return to the usual state of health	Adults with a COVID-19 diagnosis 3 months prior to the study	Cross sectional	N=213 (76.1%)	Not calculated; 90.1% under 45 years of age
34	Colizzi and al., 2022 [68]	Italy	(i) to analyze the course of mental health symptoms in COVID-19 survivors during the 12 months following the acute phase of the disease; and (ii) to identify sociodemographic and clinical predictors of post-COVID-19 mental health symptoms	Adults admitted or seen on an outpatient basis at the hospital Infectious Disease Department, with a confirmed diagnosis of COVID-19	Prospective cohort	N=479 (52.6%)	54 (σ=43–65) (median)

Table 1 (continued)

N°	Author(s) and year	Country	Main aim of the study	Study population	Study design	Sample size (% female)	Age (mean or median)
35	Martinez and al., 2021 [69]	Switzerland	To assess the frequency of persisting symptoms after COVID-19 infection in healthcare workers at a university hospital in Switzerland	Healthcare workers infected with SARS-CoV-2	Retrospective cohort	N=260 (75.4%)	Age group: 30–39
36	Uygur and al., 2021 [70]	Turkey	To obtain an initial prevalence estimate of post-COVID-19 fatigue in Turkey and identify psychological and sociodemographic risk factors associated with post-COVID-19 fatigue	People in Turkey who had recovered from COVID-19 (from a community-based survey)	Cross sectional	N=275 (58.2%)	34.67 ± 8.35 (mean)

15 were conducted in Europe, 5 in the USA, 3 in Latin America, 4 in the Middle East, 7 in Asia, and 2 in Africa. One multicenter study was conducted in Europe and the Middle East, one in India and Bangladesh, and 5 in different regions within the same country (Bangladesh, USA, India, Germany and Turkey). The study populations were adults with post-Covid syndrome, with mean ages ranging from 31.49 [48] to 56.9 [60], median ages from 28 [53] to 69 [47]. Percentage of women ranged from 8.6 [60] to 100% [46]. Sample sizes ranged from 84 [62] to 2,430,729 [35], depending on the study.

Definition and assessment of long Covid (cf Table 2)

The emergence of the long Covid syndrome being recent, its definition varies according to the studies included. However, all studies refer to the persistence or appearance of symptoms following acute infection with COVID-19, whose presence cannot be explained by an alternative diagnosis.

Depending on the study, the minimum length of time required to qualify as a post-Covid syndrome varies. Fourteen articles [36–38, 41, 43, 45, 47, 49, 50, 56, 60–62, 70] indicated symptoms for more than one month to establish long Covid syndrome, one of which [47] is based on the Centers for Disease Control and Prevention (CDC) definition. The article by Sansone et al. [51] is similar, with a duration of 3 weeks. Seven articles [35, 54, 55, 58, 66, 68, 71] used the World Health Organization (WHO) definition, i.e. the presence of symptoms developing within three months of infection with COVID-19, lasting at least two months and which cannot be explained by another diagnosis. Three articles [48, 64, 69] used the same time frame as the WHO definition, i.e. 3 months. Two studies [39, 67] used the British *National Institute for Health and Care Excellence* (NICE) definition, i.e. a clinical condition comprising both persistent COVID-19 symptomatology, with symptoms lasting from 4 to 12 weeks, and post-COVID-19 symptoms which may persist beyond 12 weeks after cure.

In the article by Tene et al. [40], long Covid was defined as the International Classification of Diseases (ICD)

post-COVID-19 diagnostic code. However, authors also introduce a time frame for subjects without formal diagnosis by a physician: a probable long Covid is the presence of post-COVID symptoms more than 4 weeks after the date of the first positive RT-PCR.

Some of the included studies did not specify the minimum time period for the onset of long Covid, but defined prolonged COVID-19 symptoms [42, 44, 46, 52, 53, 57, 63, 65].

Of the 36 studies included, 5 focused on specific symptoms of long Covid. Yavuz et al. [52] studied prolonged neurological symptoms, whereas Margalit et al. [56] and Uygur et al. [70], studied post-Covid fatigue. Magdy et al. [63], focused on persistent neuropathic pain, and Ghoshal et al. [65], studied post-Covid gastrointestinal functional disorders.

Information was collected declaratively and/or via databases and/or via scales validated in current practice and/or via medical examinations and/or via medical diagnosis and/or via questionnaires and/or via complementary examinations.

Past psychiatric and/or addiction history (cf Table 2)

Depression and anxiety

Of the 36 studies included, 14 [35, 36, 38, 42, 49, 51, 52, 54, 58, 60, 62, 63, 67, 69] looked for a history of depression or depressive symptomatology. Of these fourteen articles, six [35, 36, 38, 49, 54, 67] also studied the history of anxiety symptoms or anxiety disorders. These comorbidities were collected declaratively (9/14 or 64.28%) and/or via databases (2/14 or 14.28%) and/or via scales validated in current practice (4/14 or 28.57%) and/or via classifications of mental disorders (3/14 or 21.43%). Only one [54] of these studies examined the presence of antidepressant, hypnotic or anxiolytic medication in subjects to assess the presence of a history of depression and anxiety.

The scales used in the studies were the 4- or 9-item Patient Health Questionnaire (PHQ-4 or PHQ-9) [36, 60], the Hospital Anxiety and Depression Scale (HADS) [38] or the Beck Depression Inventory (BDI) [52]. The

Table 2 - Definitions and assessments of long covid and psychiatric history

N°	Author(s) and year	Definition of long-covid	Assessment of long-covid	Definition of psychiatric or addiction history	Assessment of psychiatric or addiction history
1	Subramanian et al., 2022 [35]	WHO definition: a history of probable or confirmed SARS-CoV-2 infection with symptoms that last for at least 2 months and can not be explained by an alternative diagnosis	Declarative	Depression/Anxiety/Smoking (ex-smoker, current smoker)/Eating disorder/Substance use disorder/Learning disability	Database of primary care medical records
2	Wang and al., 2022 [36]	Long-term COVID-19 symptoms (lasting for more than 4 weeks)	Declarative	Probable depression (subclinical or yes)/Probable Anxiety (subclinical or yes)/Current smoker	Patient Health Questionnaire (PHQ-4) Declarative
3	Grisanti and al., 2022 [37]	Signs and symptoms developed during or following a disease consistent with COVID-19 and which continue for more than four weeks but they are not explained by alternative diagnoses	Declarative	Smoking (non-smoker, smoker, ex-smoker)	Declarative
4	Garjani and al., 2022 [38]	Long-standing COVID-19 symptoms for ≥ 4 weeks	Declarative	Anxiety and/or depression	Hospital Anxiety and Depression Scale (HADS) scores
5	Craparo and al., 2022 [39]	NICE definition: a clinical condition that includes both ongoing symptomatic COVID-19 infection, where symptoms last 4 to 12 weeks, and post-COVID-19 symptoms that can persist beyond 12 weeks after recovery	Declarative	Personality traits/Alexithymia	Personality Inventory for DSM-5 Brief Form (PID-5-BF)/Toronto Alexithymia Scale-20 (TAS-20)
6	Tene and al., 2022 [40]	Definite long Covid: International Classification of Diseases (ICD) diagnosis code of post-COVID-19 Probable long Covid: post-COVID symptoms more than 4 weeks after the date of first positive RT-PCR	Diagnosed by a physician	Smoking (ever)	Declarative
7	De Oliveira and al., 2022 [41]	Persistence of at least one physical and/or mental health symptom 4 or more weeks after disease onset	Declarative	Smoking/Alcoholism	Declarative
8	Ohira and al., 2022 [42]	Persistence of symptoms after recovering from the acute phase of COVID-19	Electronic medical records and clinical summaries of patients	Depression/Schizophrenia/Asperger's spectrum syndrom	Data from medical records
9	Bai and al., 2022 [43]	Persistence of ≥ 1 physical and/or psychological symptoms for more than 4 weeks after recovery from acute illness COVID-19	Declarative, Medical examination, Scale (HADS and IES-R)	Smoking	Declarative
10	Daitch and al., 2022 [44]	Persistent symptomatology following COVID-19 infection impacting physical and cognitive functions and leading to reduced quality of life	Declarative, Questionnaire	Smoking	Declarative
11	Afroze and al., 2022 [45]	Onset or persistence of at least one self-reported symptom of COVID-19 more than 1 month	Declarative, structured clinical interview, tools	Cigarette smoking	Declarative
12	Vásconez-González and al., 2023 [46]	Persisting symptoms after COVID-19 infection	Declarative, Questionnaire	Smoke/Alcohol	Declarative
13	Frontera and al., 2022 [47]	According to Centers for Disease Control and Prevention (CDC) criteria as new or persistent symptoms occurring ≥ 4 weeks after SARS-CoV-2 infection	Declarative	Psychiatric History	Declarative

Table 2 (continued)

N°	Author(s) and year	Definition of long-covid	Assessment of long-covid	Definition of psychiatric or addiction history	Assessment of psychiatric or addiction history
14	Shukla and al., 2023 [48]	Any newly occurring or remaining symptoms or signs in COVID-19 patients after 3 months (12 weeks) of discharge from the hospital (or declared discharged in case of non-hospitalized patients)	Declarative	Smoking/Alcohol	Declarative
15	Jacobs and al., 2023 [49]	Self-reported continuing or new symptoms 28 days or more following the test date for the acute infection	Declarative	Cigarette smoking/Depression and anxiety	Declarative
16	Knight and al., 2022 [50]	Syndrome of persistent symptoms, generally for more than 4 weeks after recovery from acute COVID-19	Declarative	No psychiatric or addictive history sought	Not applicable
17	Sansone and al., 2022 [51]	Symptoms persisting for at least three weeks since positive swab test for SARS-CoV-2	Declarative	Depression/Smoking	Declarative
18	Yavuz and al., 2022 [52]	Persistence of symptoms following acute COVID-19 infection, lasting at least two months after recovery from COVID-19 Only prolonged post-COVID-19 neurological symptoms are studied	Declarative	Depression/Smoking	Declarative and Beck Depression Inventory (BDI)
19	Gutiérrez-Canales and al., 2022 [53]	Persistent symptoms for months after acute illness	Declarative	Smoking	Declarative
20	Hastie and al., 2022 [54]	WHO definition: a history of probable or confirmed SARS-CoV-2 infection with symptoms that last for at least 2 months and can not be explained by an alternative diagnosis	Declarative	Depression/Anxiety	ICD10 codes F30-F33, or antidepressant, hypnotic or anxiolytic (BNF 4.1;4.3), or self-report
21	Fleischer and al., 2022 [55]	WHO definition: a history of probable or confirmed SARS-CoV-2 infection with symptoms that last for at least 2 months and can not be explained by an alternative diagnosis	Neurological and physical examination according to standards recommended by the European Academy of Neurology including neuro-vascular, elec-trophysiological, and blood analysis. In addition, magnetic resonance imaging (MRI) and lumbar puncture if necessary	Previous psychiatric condition (Depression/Anxiety disorder/post-traumatic stress disorder/somatic disorder/adjustment disorder/borderline disorder)	Declarative
22	Margalit and al., 2022 [56]	Ongoing symptoms persisting at least 4 weeks following the onset of acute coronavirus disease 2019 Focusing in long covid fatigue in this study	physical examination by an internist, questionnaires (evaluating 14 post-Covid symptoms from 0 to 3 for intensity), cognitive fatigue task and and blood sampling	Smoking status (never, past, current)/Use of cannabis/Use of alcohol	Declarative
23	Gasnier and al., 2022 [57]	Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis	Declarative Cognitive impairment screening questionnaire from the European AIDS Clinical Society	Psychiatric History	Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Systematic interview with a psychiatrist Mini International Neuropsychiatric Interview (MINI 5.0)

Table 2 (continued)

N°	Author(s) and year	Definition of long-covid	Assessment of long-covid	Definition of psychiatric or addiction history	Assessment of psychiatric or addiction history
24	Loosen and al., 2022 [58]	WHO definition: a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis	Original diagnosis text of the physicians Following ICD-10 diagnoses were additionally used as surrogates for LCS: chronic fatigue (ICD-10: G93.3), abnormalities of breathing (ICD-10: R06), disturbances of smell and taste (ICD-10: R43), malaise and fatigue (ICD-10: R53, disturbances in attention (ICD-10: R41.8)	Depression	ICD-10: F32, F33
25	Buonsenso and al., 2022 [59]	WHO definition: Set of symptomatic sequelae that typically develop within three months of COVID-19 infection, last at least two months, and cannot be explained by alternative diagnoses	Declarative	Smoke/Alcohol	Declarative
26	Lhuillier and al., 2022 [60]	Any COVID-19-related symptoms that lasted at least 4 weeks after symptom onset	Declarative	Depressive Symptoms	Mean of depressive symptoms using the Patient Health Questionnaire (PHQ-9)
27	Tleyjeh and al., 2022 [61]	Chronic symptoms or long-term sequelae of COVID-19 lasting beyond 4 weeks after onset of symptoms	Declarative	Smoking status: Never smoked, Previous smoker, Current smoke	Declarative
28	Kidwai and al., 2022 [62]	Persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms	Declarative	Depression	Declarative
29	Magdy and al., 2021 [63]	Recovered COVID-19 (=improvement in all COVID-19 symptoms, no fever for three consecutive days and two consecutive nasopharyngeal swabs were negative for SARS-CoV-2 at a 24 h interval) adults with persistent neuropathic pain	Neurological examination validating neuropathic pain Neuropathic pain in 4 questions (DN4 \geq 4/10)	Depression/Smoking/Drug abuse	Declarative/Diagnostic and screening according to Statistical Manual of Mental Disorders (DSM-5)
30	Abdelhafiz and al., 2022 [64]	Symptoms persisting for more than 12 weeks after infection	Declarative	Smoking	Declarative
31	Ghoshal and al., 2021 [65]	Long-term gastrointestinal illness following acute COVID-19 infection	Declarative	Addiction (tobacco, alcohol)	Declarative
32	Peter and al., 2022 [66]	WHO definition: symptoms lasting for at least two months, being unexplained by an alternative diagnosis, and occurring three months from the acute infection	Declarative	Mental disorders/Smoking (current, former or never)	Declarative
33	Alkwai and al., 2022 [67]	NICE definition: signs and symptoms that develop during or after an infection, consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis	Declarative	Anxiety/Depression/Other mental health disorder	Declarative
34	Colizzi and al., 2022 [68]	WHO definition: a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis	Declarative	No psychiatric or addictive history sought	Not applicable

Table 2 (continued)

N°	Author(s) and year	Definition of long-covid	Assessment of long-covid	Definition of psychiatric or addiction history	Assessment of psychiatric or addiction history
35	Martinez and al., 2021 [69]	Symptoms persisting 90 days after COVID-19 diagnosis	Declarative	History of depression or state of exhaustion	Declarative
36	Uygur and al., 2021 [70]	Symptoms that persist for 28 days after a COVID-19 diagnosis This study focuses on post-Covid fatigue	Declarative	History of psychiatric disease/ History of psychiatric drug	Declarative

PHQ-4 is an autoquestionnaire including a 2-item depression measure (PHQ-2) and a 2-item anxiety measure (GAD-2), with answers ranging from 0 (not at all) to 3 (almost every day). Scores of 3 or more on the PHQ-2 or GAD-2 indicated probable depression or anxiety. The PHQ-9 scale is the same as above, but with 9 items to assess depression. These scales, which assess the presence of depressive and anxiety symptoms (for the Wang et al. study) during the previous 2 weeks, were administered before the onset of the post-Covid syndrome. The HADS scale is a self-administered questionnaire that screens separately for anxiety and depressive disorders, using two scores (ranging from 0 to 21 for each score). Participants with a HADS score ≥ 11 are considered likely to suffer from anxiety or depression. This scale was administered before the onset of long Covid syndrome in the participants. The BDI is a questionnaire consisting of a total of 21 items and provides a score between 0 and 63, with a higher score indicating the presence or severity of depression.

Depression was defined in two studies by diagnostic codes (F32, F33 for Loosen et al. [58] and F30-F33 for Hastie et al. [54]) of the International Classification of Diseases (ICD-10). Magdy et al. [63] assessed depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for persistent depressive disorders, which require the presence of depressive symptoms over a period of at least 2 years.

The proportion of long Covid subjects with a history of depression ranged from 5% [69] to 53.4% [36] in eight studies. In most cases (6/8 or 75%), they find a proportion more than 10% (Fig. 3).

Lhuillier et al. in 2022 [60] was interested in the mean number of pre-existing depressive symptoms, which was higher in long Covid subjects than in those who had not developed a post-Covid syndrome (4.23 versus 3.06), but this difference was not significant ($p=0.609$).

The proportion of subjects with a history of anxiety among those with long Covid varies from 13% [67] to 53.3% [36] depending on the study (Fig. 4).

The proportion combining a history of anxiety and depression was documented in 2 studies and ranged from 13.7 [49] to 54.3% [38] (Fig. 5).

The proportion of subjects with a history of anxiety and/or depression, when compared to a group with or without long Covid, was significantly higher in long Covid group. The difference in proportion for anxiety and depression between groups with and without long Covid was not significant in the study by Alkwaï et al. alone [67] ($p=0.055$ for depression and 0.056 for anxiety).

Smoking

Cigarette smoking was the most frequently researched addictive comorbidity, appearing in 21 articles [35–37, 40, 41, 43–46, 48, 49, 51–53, 56, 61, 63–66, 71]. The information was collected on a declarative basis, except for one article where it was obtained from a primary care database [35]. No publication specifies the quantity and type of tobacco consumption, except one [56] which estimates consumption in pack-years (PY) among active smokers: average consumption was 14.09 PY in subjects with post-Covid fatigue, compared with 12.29 PY in subjects without fatigue, but this difference was not significant ($p=0.936$). Some studies distinguished between active and weaned smokers.

Overall, the proportion of active smokers varied from 8.3% [35] to 52.5% (but this high value is explained by the grouping of occasional and regular smokers) [49] (Fig. 6). The 6 studies [35–37, 43, 50] investigating the proportion of former smokers found a percentage ranging from 4.2% [43] to 55% [37] (Fig. 7).

The precision of the proportion in long Covid subjects was not always indicated. One article compared proportions of alcohol and tobacco addiction without dissociating the two uses among the subjects, which is 20% [65]. This proportion does not differ statistically between subjects with or without long Covid ($p=0.55$).

There were no significant differences in the proportions of participants with and without post-Covid syndrome in 7 articles [41, 49, 56, 63–65, 71] of the 14 articles reporting the proportion among long Covid subjects.

Alcohol use disorders and other addictions

Six studies [41, 46, 48, 56, 65, 71] assessed alcohol consumption among participants in a declarative manner. However, only one of these articles defined for dependence, using the term "addiction" [65]. The other

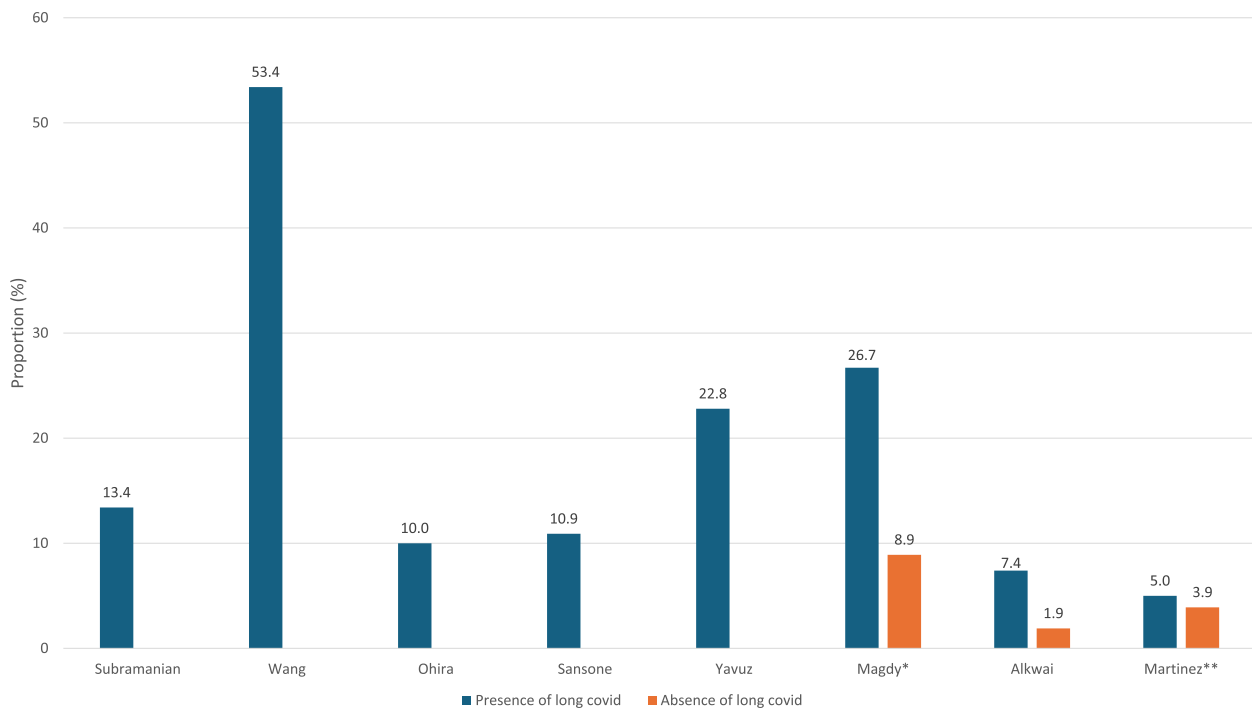


Fig. 3 Proportion of history of depression in subjects with and without long covid, when specified in studies (* $p < 0.05$, ** $p < 0.01$)

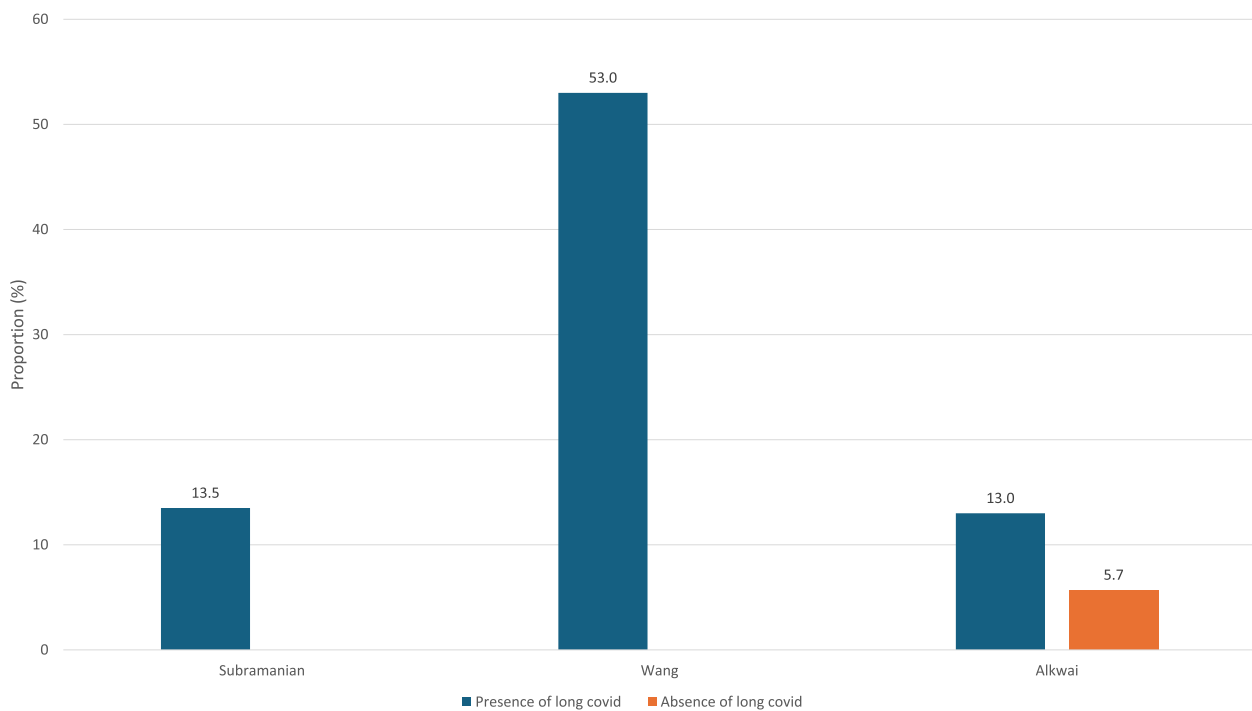


Fig. 4 Proportion of history of anxiety in subjects with and without long covid, when specified in studies

publications only assessed consumption, even occasional, without use disorder.

The proportion of alcohol consumption, even occasional, varied from 8.9% [41] to 67.7% [71] within the studies (Fig. 8). The average number of alcoholic drinks

per week was investigated in one study [56] and was 1.1 versus 1.4 in subjects without a long Covid, but this difference was not significant ($p = 0.247$). Ghoshal et al. [65], introduced the term "addiction" also including smoking, is discussed in the previous section.

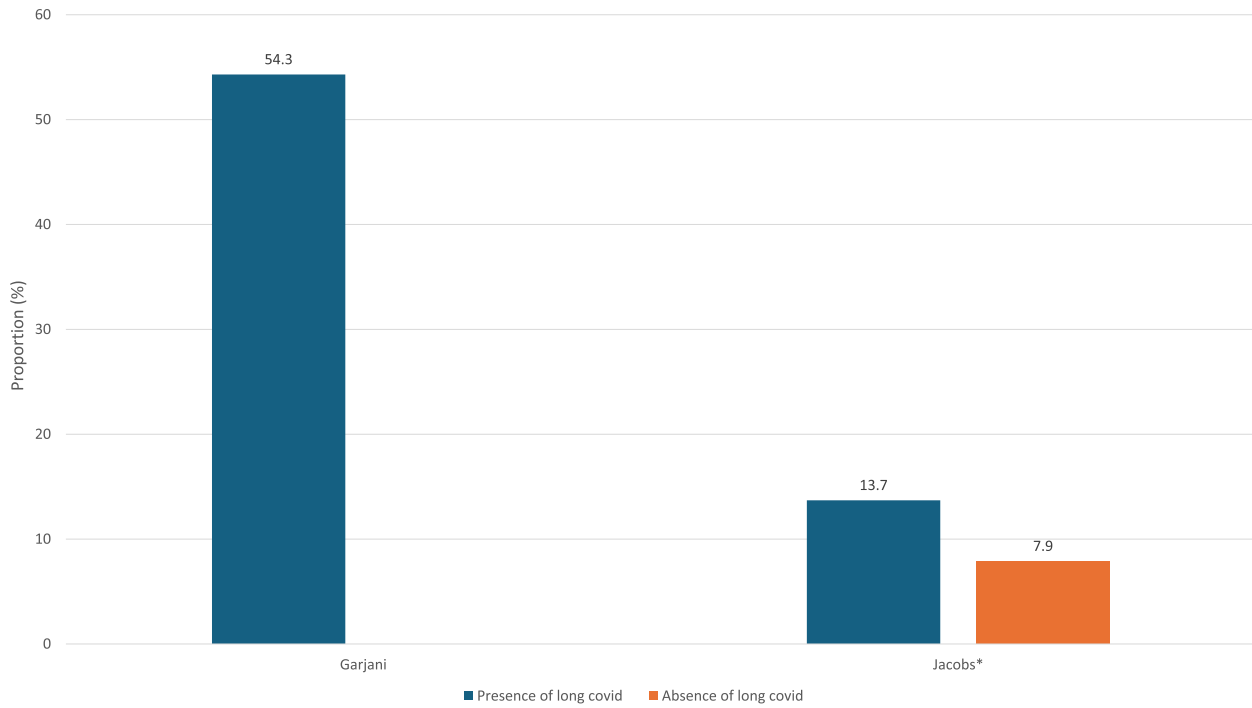


Fig. 5 Proportion of history of anxiety and depression in subjects with and without long covid, when specified in studies (* $p < 0.05$)

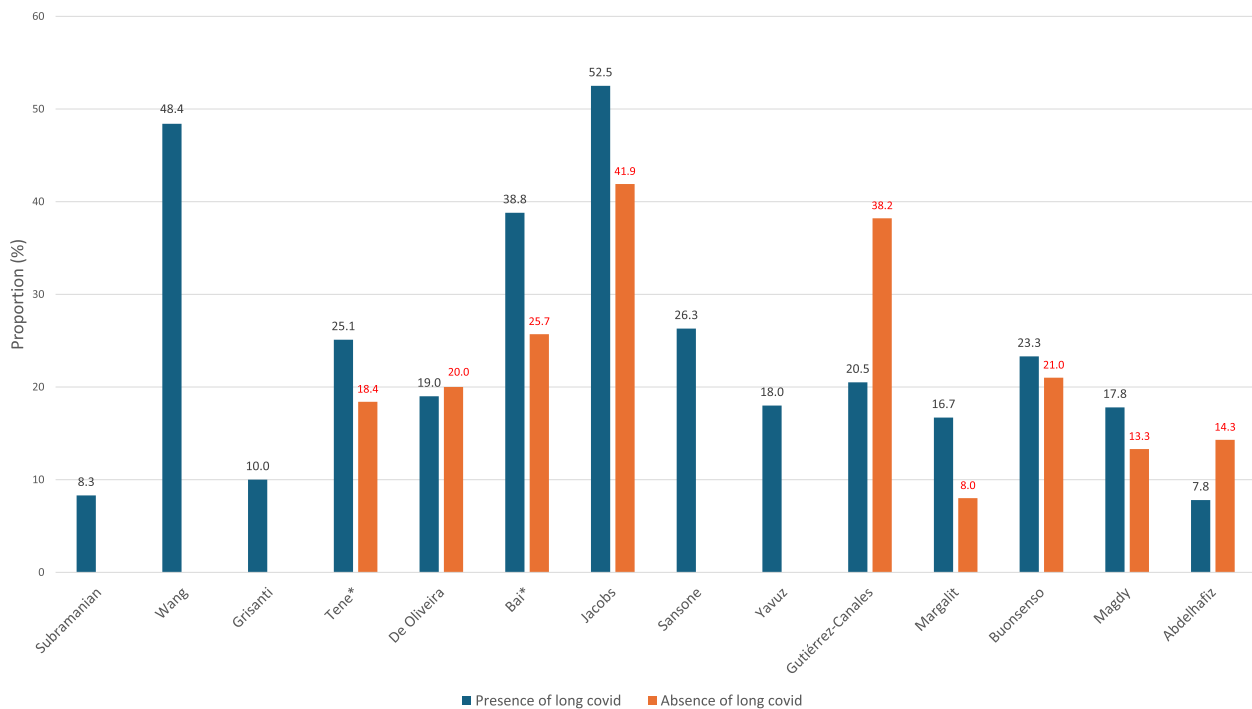


Fig. 6 Proportion of smoking in subjects with and without long covid, when specified in studies (* $p < 0.05$)

Cannabis use, assessed on a declarative basis, was also studied by Margalit et al. [56]: there was 7.7% in long Covid subjects with fatigue, but no significant difference with subjects without long Covid ($p = 0.473$).

Subramanian et al. [35] studied substance use disorder, assessed using a medical database, and found a proportion of 12% among long Covid subjects. The notion of drug abuse, without further details, was also sought in a study [63] among subjects on a declarative basis, with

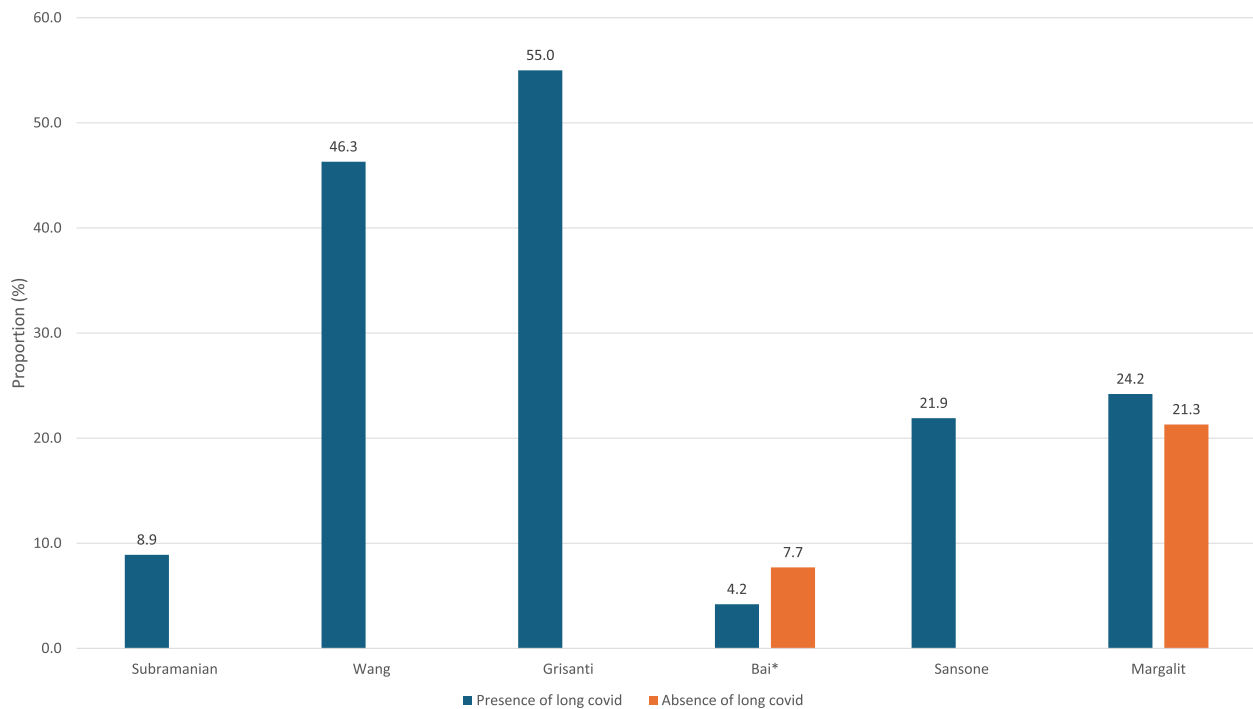


Fig. 7 Proportion of former smokers in subjects with and without long covid, when specified in studies (* $p < 0.05$)

a proportion of 2.2%, among the Covid long population, but there was no significant difference with subjects without long Covid ($p = 0.315$).

Other past psychiatric history

Nine articles [35, 39, 42, 47, 55, 57, 66, 67, 70] looked for past psychiatric history other than or in addition to anxiety-depressive disorders. Information was collected declaratively, except by Subramanian et al. [35], who used a primary care database.

Subramanian et al. [35] focused on eating disorders and learning disorders, and found a proportion of 14.5% and 9% respectively among Covid long subjects.

Ohira et al. [42] also specified subjects suffering from schizophrenia and participants with Asperger's syndrome, both at 2.2%, in long Covid subjects only.

Four studies looked for general psychiatric history among their subjects, without distinguishing between subtypes of mental disorder. Gasnier et al. [57] found 3.95% subjects with a history of psychiatric disorders among long Covid subjects, and Uygur et al. [70] found 24.5% among long Covid subjects (versus 3.3% for subjects without prolonged symptoms, $p < 0.01$). Also, in this study [70], around 1/3 of long Covid subjects had already received psychotropic treatment (versus 6.7% in subjects without prolonged symptoms, $p < 0.01$).

Fleischer et al. [55] focused solely on subjects with post-COVID-19 syndrome. They found an overall proportion of psychiatric history of 19%. The subtypes were: depression (66.7%), anxiety disorders (20.1%),

post-traumatic stress disorder (3.3%), somatoform disorder (3.3%), adjustment disorder (3.3%), borderline disorder (3.3%). However, these sub-categories were not included in the statistical analysis.

Alkwai et al. [67] examined other mental disorders (unspecified) in addition to anxiety-depressive disorders, their proportion being 3.7% in subjects with long Covid. However, there was no significant difference between the two groups ($p = 0.064$).

Personality traits and the degree of alexithymia were studied by Craparo et al. [39], using 2 separate scales validated for current practice. These are the DSM-5 Personality Inventory (PID-5-BF) and the Toronto Alexithymia Scale-20 (TAS-20). The PID-5-BF is a 25-item self-report questionnaire that assesses personality traits according to five personality models: negative affectivity (including anxiety, separation anxiety and emotional lability), detachment (defined as withdrawal, anhedonia and avoidance of intimacy), antagonism (including manipulation, deception and grandiosity), disinhibition (including irresponsibility, impulsivity and distraction) and psychoticism (characterized by eccentricity and unusual beliefs and experiences). The subject is asked to rate each statement (e.g. "People would describe me as reckless") on 4 levels from 0 (very false or often false) to 3 (very true or often true), depending on which corresponds to him or her. The TAS-20 is a 20-item self-evaluation questionnaire used to assess the presence of alexithymia. Alexithymia is characterized by an inability to recognize or describe one's emotions, due to a lack of awareness of

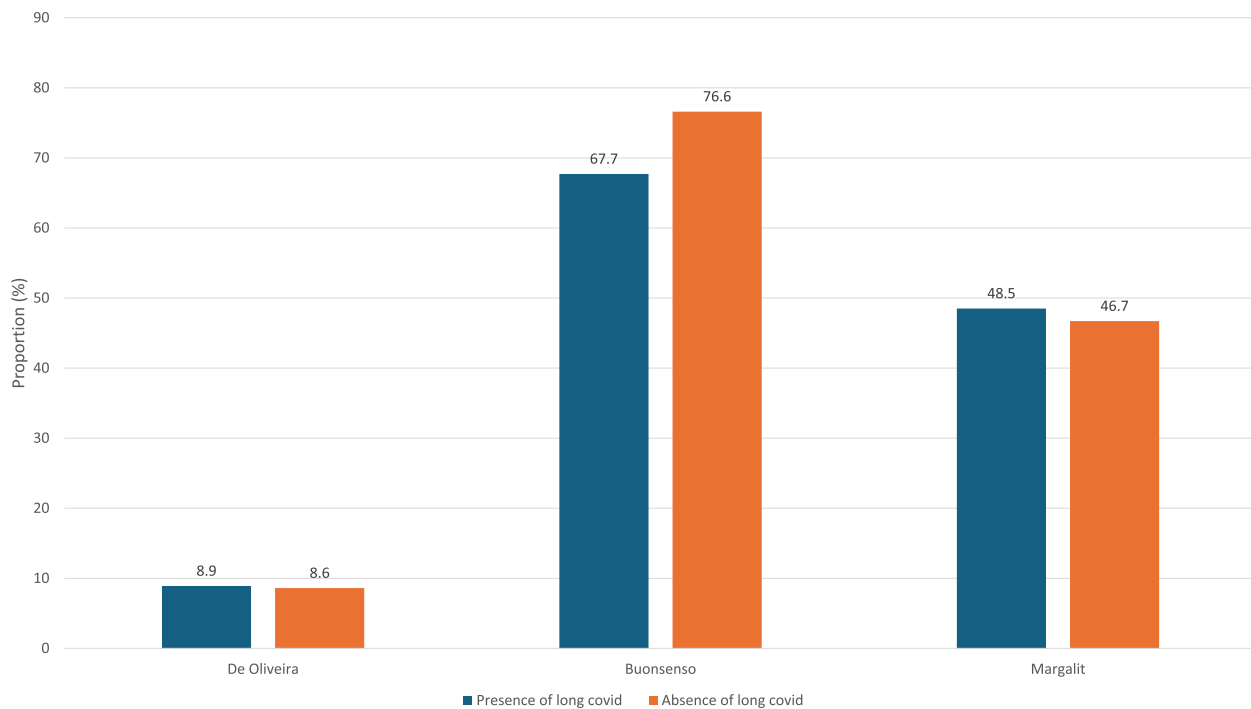


Fig. 8 Proportion of alcohol consumption in subjects with and without long covid, when specified in studies

one's emotional states. For each item (e.g., "I often don't see my feelings clearly"), participants are asked to rate their agreement with the sentence on 5 levels, from 1 (strongly disagree) to 5 (strongly agree). In addition to the total alexithymia score, it is possible to calculate scores for the three main dimensions of alexithymia: difficulty in identifying feelings, difficulty in describing feelings, and outward-oriented thinking. In this article, the various personality traits and the three dimensions of alexithymia were analyzed in long Covid subjects grouped according five types of symptoms: no symptoms, brain fog, respiratory disorder, sensory disorder and multiple disorder. However, no predominant personality categories were specified for these groups. There were no results on degrees of alexithymia according to groups in their publication, thus limiting interpretation. On the other hand, statistical tests were carried out to study their possible associations with the presence of the Covid long clusters, which will be described in greater detail below.

Relationship between past psychiatric and/or addiction history and long Covid Cf Table 2

Depression and anxiety

The various results concerning the link between a history of depression and the evolution of COVID-19 symptomatology are summarized in Fig. 9.

Subramanian et al. [35] found an increased risk of long Covid with an aHR of 1.31 (95% CI=1.27–1.34) for depression and an aHR of 1.35 (95% CI=1.31–1.39) for anxiety ($p < 0.05$). Jacobs et al. [49] also showed a link

between a history of anxiety and/or depression and the development of long Covid, with an OR of 1.72 (95% CI=1.17–2.52, $p < 0.05$). Similarly, depression was found to be a risk factor for the development of the syndrome by Loosen et al. [58] (OR 1.21, 95% CI=1.07–1.37). Martinez et al. [69] showed that the existence of depression or burn out prior to Covid was associated with persistence of symptoms after 3 months (OR 4.16, 95% CI=1.64–10.56, $p = 0.003$). Yavuz et al. in 2022 [52] focused on a long Covid population with prolonged neurological symptoms who consulted a specialized center. This study found a significant difference ($p < 0.001$) in the history of depression, greater in patients with prolonged neurological symptoms. This was identified as an independent risk factor in the multivariate analysis of this persistent neurological symptomatology (OR=4.54, 95% CI=1.88–10.96, $p = 0.001$).

Wang et al. [36] found that probable premorbid depression and anxiety increased the risk of developing post-COVID-19 syndrome (RR 1.39, 95% CI 1.19–1.63 and RR 1.47, 95% CI 1.27–1.70, $p < 0.001$, respectively). Furthermore, participants with more than 2 types of distress (i.e. depression, anxiety, worry, perceived stress, loneliness) had a higher risk of developing a post-COVID-19 syndrome (≥ 2 types vs. none, RR 1.54, 95% CI 1.28–1.86, $p < 0.001$). All COVID-19 symptoms, with the exception of persistent cough and problems with smell or taste, were more frequent in participants with each type of distress. In addition, those suffering from distress at the start of the study reported a greater number of symptoms

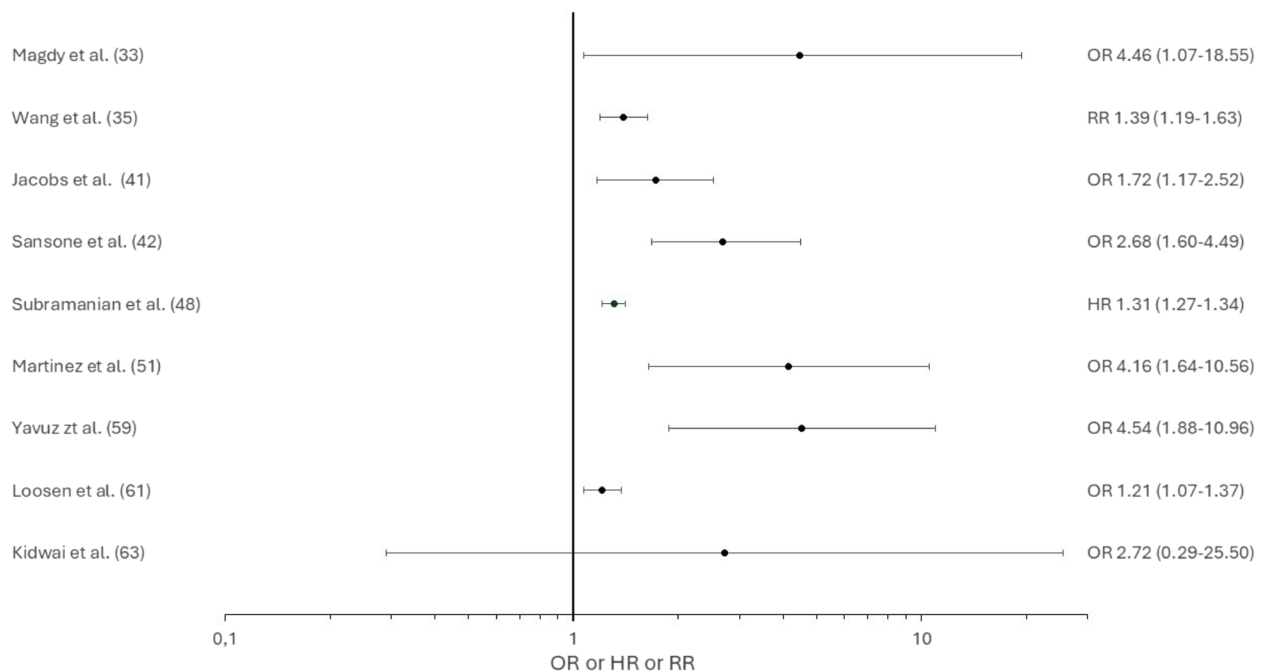


Fig. 9 Description of the results of the included studies concerning the link between a history of depression and the evolution of covid symptomatology

of the post-COVID-19 condition (e.g. probable depression, mean [σ] of symptoms = 3.4 [2.1]; no depression, mean [σ] of symptoms = 2.5 [1.7]). symptoms of depression, anxiety, perceived stress and worry at baseline were associated with a 25–51% increased risk of having symptoms that interfered with occasional or regular activities.

According to Garjani et al. [38], subjects with a history of depression and/or anxiety are less likely to recover from acute Covid infection (aHR 0.708, 95% CI 0.533–0.941, $p < 0.05$). These findings are confirmed by Hastie et al. [54], who found that lack of complete remission was associated with pre-existing Covid anxiety/depression (OR 2.29 with 95% CI = 2.06–2.55 for lack of recovery and OR 1.66 with 95% CI = 1.58–1.55 for partial recovery, $p < 0.05$).

Several articles focused more specifically on the role of anxiety-depressive factors on the persistence of certain symptoms of long Covid. For example, Lhuillier et al. [60] showed that depressive symptoms were associated with post-Covid respiratory sequelae in bivariate analysis, but the results are non-significant in multivariate analysis (although they do not specify the variables used for adjustment). Magdy et al. [63] on participants with post-Covid pain found a significantly higher incidence of pre-morbid depression in cases of post-COVID-19 pain than in the control group ($p = 0.027$). Depression was found to increase the incidence of post-COVID-19 pain by 4.462 (95% CI = 1.073–18.553, $p = 0.04$).

All subjects with pre-existing depression complained of dysautonomic symptoms (defined as fatigue, confusion, insomnia or impaired concentration) in the Sansone et al.

study [51]. The main risk factor for prolonged psychiatric symptoms was the presence of a history of depression (aOR = 6.35, 95% CI = 2.01–20.11, $p < 0.05$). It was also found that the duration of symptoms lasting more than 200 days increased with the presence of a pre-existing depressive syndrome (aOR = 2.68, 95% CI = 1.60–4.49, $p = 0.001$).

According to Ohira et al. [42], the most frequent comorbidity with long Covid was depression (nine patients, 10.0%, 95% CI = 4.6–17.6). Eight patients (8.9%, 95% CI = 3.0–14.7) suffered from a psychiatric illness other than depression.

Only the study by Kidwai et al. [62] showed no significant causal relationship.

Smoking

Subramanian et al. [35] showed that both active and occasional smoking increased the risk of developing a long Covid (aHR 1.12, 95% CI 1.08–1.15 and 1.08, 95% CI 1.05–1.11, respectively, $p < 0.05$). This increased risk was confirmed by Tene et al. [40] (aOR = 1.532, 95% CI 1.358–1.727, $p < 0.05$). Bai et al. [43] established that active smokers (aOR 0.19 for ex-smokers vs. active smokers, 95% CI 0.06–0.62, $p = 0.002$) were at greater risk of prolonged Covid symptoms. Being a former smoker was an unfavourable factor for returning to the initial state of health (OR 1.23 95% CI 1.05–1.45, $p = 0.012$) according to Tleyjeh et al. [61], but this was not demonstrated in active smokers, with a non-significant result on analysis ($p = 0.975$).

However, there was no consensus on these results. Indeed, Yavuz et al. [52], found that the rate of smokers was lower in the group with prolonged neurological symptoms (PNS) than in the group without PNS ($p=0.047$). In the univariate analysis, being a non-smoker increased the risk of PNS (OR 1.93, 95% CI 1.116–3.22, $p=0.016$), but this result was not confirmed in the multivariate analysis. Smoking was also observed in greater proportion in the asymptomatic group (20.5% in long Covid subjects versus 38.2%, OR=0.42, 95% CI 0.21–0.82, $p=0.012$) by Gutiérrez-Canales et al. [53].

Daitch et al. [44], Sansone et al. [51], Shukla et al. [48], Abdelhafiz et al. [64] and Wang et al. [36] did not find significant association between smoking and post-Covid syndrome.

Some articles studied more specifically certain symptoms or clusters of long Covid. Magdy et al. [63] showed no significant effect of smoking on the onset of post-COVID-19 pain ($p=0.561$). Afroze et al. [45] show that smoking is an independent risk factor (OR 1.69, 95% CI 1.05–2.73, $p<0.05$) for neurological symptoms (defined in the article as peripheral neuropathy, anosmia, absence/alteration of taste, tremor). According to Peter et al. [66], smoking (particularly active smoking status) also appeared to be a risk factor for several symptom groups. Vásquez-González et al. [46] focused on a population of pregnant women compared with non-pregnant women. Pregnant women who smoked were found to have a higher risk of fatigue than the non-pregnant group (OR 114, 95% CI 3.85–3395). However, in general, when all symptoms were studied, no statistically significant difference was found between long Covid symptoms in smokers and non-smokers in this study.

Some authors looked for the presence of smoking in participants, but did not perform statistical analysis for its possible association on the onset of long Covid [37, 41, 65, 71].

Alcohol use disorder and other past addictive histories

Three articles [41, 56, 65] did not perform a statistical analysis of the relationship between addictive history (other than tobacco) and the development of long Covid. No statistically significant difference was found when considering alcohol consumption as a risk factor for the development of a long Covid syndrome according to Vásquez-González et al. [46]. Alcohol consumption did not significantly increase the risk of sequelae according to Shukla et al. [48] ($p=0.163$). Substance abuse had no significant effect on the onset of post-COVID-19 pain according to Magdy et al. [63] ($p=0.315$). Only Subramanian et al. [35] found an increased risk with substance use disorders (aHR 1.15, 95% CI 1.07–1.23).

Other past psychiatric history

According to Subramanian et al. [35], eating disorders and learning disabilities increased the risk of developing a long Covid syndrome (aHR 1.16, 95% CI 1.06–1.27 and aHR 1.24, 95% CI 1.11–1.40 respectively).

Frontera et al. [47] showed that a history of psychiatric illness prior to COVID-19 was associated with worse mRS (modified Rankin scale) and Barthel scores at 6 months (OR 1.94, 95% CI 1.03–3.66, $p=0.040$ and OR 2.23, 95% CI 1.07–4.64, $p=0.032$ respectively). These scores are commonly used in the aftermath of stroke to assess the functional consequences on the subject's life. The modified Rankin Scale assesses functional status and disability (mRS; 0=no symptoms, 6=death, dichotomized into 0–3 vs. 4–6). The Barthel index assesses activities of daily living (0=completely dependent, 100=independent for all activities). In another study [55], subjects with a psychiatric history were more likely to report psychiatric symptoms (OR 3.5, 95% CI 1.47–8.32, $p<0.01$), fatigue (OR 2.43, 95% CI 1.11–5.82, $p<0.05$), or difficulty concentrating (OR 2.58, 95% CI 1.01–6.19, $p<0.05$). A subgroup analysis of patients with a psychiatric history showed significantly higher total fatigue scores compared to patients without a psychiatric history. It is also interesting to note that, patients with psychiatric comorbidities had a higher risk of somatization compared to patients without a history of psychiatric disorder. Peter et al. [66] showed that pre-existing mental disorders were associated with the onset of any symptom and with many different symptom groups.

With regard to personality traits [39], antagonism was found to be a significant risk factor for brain fog (OR=0.64, $p=0.01$), respiratory disorders (OR=0.65, $p=0.04$) and sensory disorders (OR=0.66, $p=0.03$). Alexithymia, specifically difficulty in identifying emotions, was also a risk factor for multiple disorders (OR=3.87, $p<0.001$), respiratory disorders (OR=3.17, $p<0.001$), and brain fog (OR=2.05, $p<0.001$).

Psychiatric symptoms during the acute phase of Covid (cf Table 3)

Only one study [68] out of all the selected publications investigates the presence of psychiatric symptoms during the acute phase of COVID-19, defined as depression, anxiety, insomnia, impaired concentration and attention, and fatigue. The presence of these symptoms at the start of the illness increased the risk of developing concentration and attention disorders one year after contracting COVID-19 (OR=2.09, 95% CI=1.25–3.49, $p=0.005$).

Psychological experience of acute infection in long Covid patients (cf Table 3)

Of the 35 articles in our review, three studies [36, 39, 50] investigated the psychological experience of the acute

infection. Knight et al. [50] and Wang et al. [36] looked at the psychological impact of the acute phase, using two distinct methods. In the first, patients were asked "Did you have a negative psychological experience of the acute Covid infection? The second involves asking the patient to rate his or her level of concern about acute covid infection on 4 levels ranging from "not at all concerned" to "very concerned", with a negative experience defined by the last 2 levels. Wang's study also uses the Perceived Stress Scale 4 (PSS-4) to assess the psychological experience of the initial infection. It is based on 4 questions and assesses feelings and thoughts over the past month. In each case, subjects are asked to indicate the frequency, in 5 levels (ranging from "never" to "very often"), with which they felt the situation indicated (e.g. "Over the past month, how often have you felt that you were unable to control the important things in your life?"). The results of this scale were divided into quartiles, the upper quartile being considered a negative psychological impact of the acute infection.

Overall, participants with persistent symptoms had a significantly higher negative psychological experience than those without persistent symptomatology. Indeed, 52.3% of long Covid subjects reported a bad experience, compared with 24.5% of those without sequelae ($p < 0.001$) [50]. This trend is confirmed by Wang et al. [36], which showed that being "very worried" about COVID-19 (RR 1.43, 95% CI 1.22–1.68, $p < 0.001$) and being in the upper quartile of the perceived stress scale (RR 1.50, 95% CI 1.21–1.86, $p < 0.001$) significantly increased the risk of post-COVID-19 syndrome.

Craparo et al. [39] assessed the experience of acute COVID-19 infection according to post-traumatic elements measured by the Impact of Events Scale-Revised (IES-R) at the time of the study. This scale is a 22-item self-report questionnaire designed to assess post-traumatic symptomatology following unexpected exposure to death, threat to life or threat to physical or mental integrity. It was adapted to the specific COVID-19 event (e.g., "Any reminder that brings back feelings related to COVID-19"). The symptoms studied were neurovegetative hyperreactivity, avoidance behaviors and intrusion. Their associations with brain fog, respiratory disorders, sensory disorders and multiple disorders of the post-Covid syndrome were investigated. Hyperreactivity was a significant predictor of brain fog (OR = 2.54, 95% CI 1.45–4.39, $p < 0.001$), respiratory disorders (OR = 2.33, 95% CI 1.19–4.44, $p = 0.01$) and sensory disorders (OR = 2.16, 95% CI 1.17–3.94, $p = 0.01$). The rest were non-significant.

Quality of included studies (Fig. 10)

The case-controls were of good quality, with an NOS score of 8 for the three studies. For the cohort studies,

four were of average quality, with a NOS score of 6, twelve were of good quality, with a score of 7 for eight articles and 8 for four, and one was of very good quality. Cross-sectional studies received a NOS score ranging from 5 to 9: seven studies were of average quality; seven studies were of good quality and two studies were of very good quality. In all, 11 studies were of average quality, 22 of good quality and 3 of very good quality. The assessment of NOS criteria is specified in Table 4.

Discussion

This systematic review, based on the above-mentioned search strategies and selection criteria, identified 36 studies concerning the link between long covid and past psychiatric history. These included case-control, cohort and cross-sectional studies. The quality of the studies according to the NOS scale ranged from 5 to 9 for cross-sectional studies, 6 to 9 for cohort studies, and case-control studies had a total score of 8 out of 9.

Regarding the definition chosen for long Covid syndrome, the most frequently was a persistence of symptoms beyond one month after an acute COVID-19 infection whose presence could not be explained by an alternative diagnosis. This post-Covid syndrome was mainly assessed by declarative means and medical examinations. The most frequently sought psychiatric and addictive histories were anxiety disorders, depression and smoking, based mainly on self-report and sometimes on scales used in everyday practice.

Our review highlights an overall high proportion of a history of anxiety and/or depressive disorder among subjects presenting with post-Covid syndrome, compared with the worldwide prevalence of 5% for depressive disorders and 4% for anxiety disorders according to the WHO in 2018 [72, 73]. Although the last five years have seen an increase in prevalence of 3 and a half percentage points on a more local scale such as France [74], the proportions with a history of anxiety and depression remain high overall compared with the global population. However, depending on the study, a very wide variation in percentages has been observed. This is partly due to differences in methods. Martinez et al. [69], where the proportion was lowest, assessed history on a declarative basis, which could lead to recall bias. Wang et al. [36], where the proportion was highest, detected history of depression using a scale of 4 questions, which could lead to overestimation of depression. The majority of the articles included also used self-questionnaires [36, 38, 52, 60], thus increasing the variability of the results, which could have been improved by using hetero-questionnaires. This variation can also be explained by the type of population studied, as in the study by Garjani et al. [38], where the proportion of anxiety and/or depressive disorders was approximately 50%, in people with multiple sclerosis. However, it

Table 3 Assessment of psychiatric symptoms and psychological experience of initial infection, and proportion of psychiatric history

N°	Author(s) and year	Outcome for psychiatric symptoms during acute COVID	Assessment of psychiatric symptoms in the acute phase of COVID	Outcome for psychological experience of infection	Proportion of psychiatric and/or addictive histories among long covid patients
1	Subramanian et al., 2022 [35]	Not researched	Not researched	Not researched	Depression: 13.4% Anxiety: 13.5% Smoking (never smoked 6.8%, ex-smoker 8.9%, current smoker 8.3%) Eating disorder: 14.5% Substance use disorder: 12% Learning disabilities: 9%
2	Wang and al., 2022 [36]	Not researched	Not researched	Declarative: Very worried and somewhat worried about Covid-19 Perceived Stress Scale (PSS-4)	Probable depression: yes (53.4%), subclinical symptoms (48.1%) Probable anxiety: yes (53%), subclinical symptoms (46.5%) Smoking: active (48.4%), former (46.3%)
3	Grisanti and al., 2022 [37]	Not researched	Not researched	Not researched	Smoker (10%), ex-smoker (55%)
4	Garjani and al., 2022 [38]	Not researched	Not researched	Not researched	Anxiety and/or depression (long-standing COVID-19 symptoms for ≥ 4 weeks): 50.4% Anxiety and/or depression (long-standing COVID-19 symptoms for ≥ 12 weeks): 54.3%
5	Craparo and al., 2022 [39]	Not researched	Not researched	Impact of Event Scale-Revised (IES-R)	Not researched
6	Tene and al., 2022 [40]	Not researched	Not researched	Not researched	Smoking: 25.1%
7	De Oliveira and al., 2022 [41]	Not researched	Not researched	Not researched	Smoking: 19% Alcoholism: 8,9%
8	Ohira and al., 2022 [42]	Not researched	Not researched	Not researched	Depression: 10% Schizophrenia: 2,2% Asperger's spectrum syndrom: 2,2%
9	Bai and al., 2022 [43]	Not researched	Not researched	Not researched	Active smokers (38,8%), ex-smokers (4,2%)
10	Daitch and al., 2022 [44]	Not researched	Not researched	Not researched	Not specified in long covid subjects
11	Afroze and al., 2022 [45]	Not researched	Not researched	Not researched	Not specified in long covid subjects
12	Vásconez-González and al., 2023 [46]	Not researched	Not researched	Not researched	Not specified in long covid subjects
13	Frontera and al., 2022 [47]	Not researched	Not researched	Not researched	Not specified in long covid subjects
14	Shukla and al., 2023 [48]	Not researched	Not researched	Not researched	Not specified in long covid subjects
15	Jacobs and al., 2023 [49]	Not researched	Not researched	Not researched	Depression and anxiety : 13,7% Cigarette smoking occasionally or regularly: 52,5%
16	Knight and al., 2022 [50]	Not researched	Not researched	Declarative: negative psychological impact (yes/no)	Not researched
17	Sansone and al., 2022 [51]	Not researched	Not researched	Not researched	Smokers (26.3%), Ex smokers (21.9%) Depression: 10.9%
18	Yavuz and al., 2022 [52]	Not researched	Not researched	Not researched	Depression: 22.8% Smoking: 18%
19	Gutiérrez-Canales and al., 2022 [53]	Not researched	Not researched	Not researched	Smoking: 20.5%
20	Hastie and al., 2022 [54]	Not researched	Not researched	Not researched	Not specified in long covid subjects

Table 3 (continued)

N°	Author(s) and year	Outcome for psychiatric symptoms during acute COVID	Assessment of psychiatric symptoms in the acute phase of COVID	Outcome for psychological experience of infection	Proportion of psychiatric and/or addictive histories among long covid patients
21	Fleischer and al., 2022 [55]	Not researched	Not researched	Not researched	Previous psychiatric condition: 19% (Depression: 66.7% Anxiety disorder: 20.1% Post-traumatic stress disorder: 3.3% Somatic disorder: 3.3% Adjustment disorder: 3.3% Borderline disorder: 3.3%)
22	Margalit and al., 2022 [56]	Not researched	Not researched	Not researched	Smoking status: past (24.2%), current (16.7%) Use of cannabis: 7.7% Use of alcohol: 48.5%; Alcohol servings per week: 1,1 (mean)
23	Gasnier and al., 2022 [57]	Not researched	Not researched	Not researched	Past psychiatric disorder: 3,95%
24	Loosen and al., 2022 [58]	Not researched	Not researched	Not researched	Not specified in long covid subjects
25	Buonsenso and al., 2022 [59]	Not researched	Not researched	Not researched	Smoke (yes): 23.3% Alcohol (yes): 67.7%
26	Lhuillier and al., 2022 [60]	Not researched	Not researched	Not researched	Depressive Symptoms Mean (SD): 4.23 (4.71) in Post-Acute COVID-19 Sequelae (vs 3.06 in no post acute covid sequelae)
27	Tleyjeh and al., 2022 [61]	Not researched	Not researched	Not researched	Not specified in long covid subject
28	Kidwai and al., 2022 [62]	Not researched	Not researched	Not researched	Not specified in long covid subject
29	Magdy and al., 2021 [63]	Not researched	Not researched	Not researched	Depression: 26.7% Smoking: 17.8% Drug abuse: 2.2%
30	Abdelhafiz and al., 2022 [64]	Not researched	Not researched	Not researched	Smoking: 7.78%
31	Ghoshal and al., 2021 [65]	Not researched	Not researched	Not researched	Addiction (tabac, alcool): 20%
32	Peter and al., 2022 [66]	Not researched	Not researched	Not researched	Not specified in long covid subject
33	Alkwai and al., 2022 [67]	Not researched	Not researched	Not researched	Anxiety: 13% Depression: 7.4% Other mental health disorder: 3.7%
34	Colizzi and al., 2022 [68]	Mental health symptoms: symptoms of psychiatric disorders (depression, anxiety, insomnia), lack of concentration and focus, and fatigue	Declarative	Not researched	Not researched
35	Martinez and al., 2021 [69]	Not researched	Non recherché	Not researched	History of depression or state of exhaustion: 5%
36	Uygur and al., 2021 [70]	Not researched	Not researched	Not researched	Fatigue group: History of psychiatric disease (24.5%); History of psychiatric drug use (31%)

has been found that anxiety-depressive comorbidities are frequent in these patients [75, 76].

Concerning smoking, this review found important variations between the studies. This can be explained by the geographical area of the populations studied. For example, the lowest rates of smoking were found in the UK, and the highest rates in the USA, which is consistent with epidemiological data [77]. This variation can also be explained by the methods used. Indeed, Jacobs et al.

[49] found high rates because there was no distinction between regular and occasional smokers. Concerning alcohol consumption, rate was not significantly different from subjects without long Covid. This may be explained by the fact that the studies did not investigate the type and frequency of alcohol consumption.

Other addictive histories and psychiatric disorders cannot be interpreted given the little data in all our included studies.

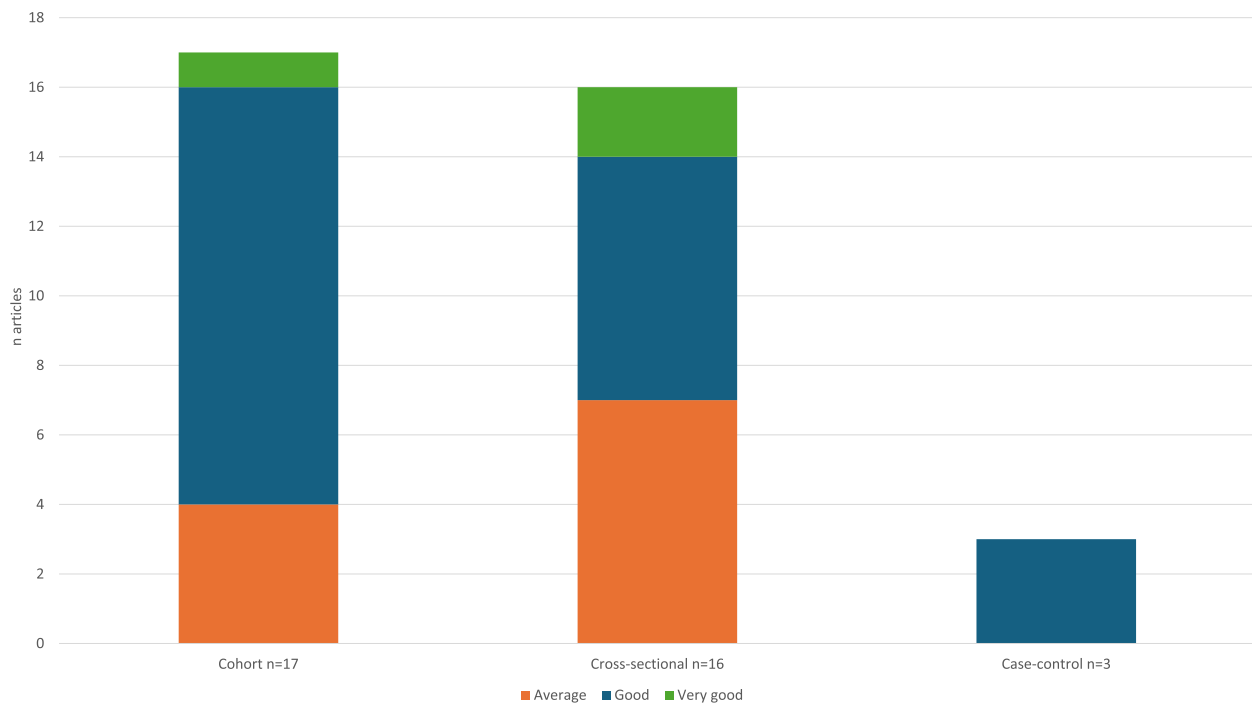


Fig. 10 Quality of included studies

Depression and anxiety appear in this review as potential predictive factors in the development of a post-Covid syndrome. Other mental disorders (i.e. schizophrenia, Asperger's syndrome, eating disorders, learning disorders and unspecified others) could increase the risk of developing a long Covid but there is not enough data. The influence of psychiatric disorders had already been identified in other reviews of the overall risk factors for this syndrome [78, 79]. In an increasingly preventive medicine, it seems important to identify populations at risk. Health professionals working with individuals can ask about any symptoms that may be beginning to appear, such as anxiety, stressful life events or social isolation that may favour a psychiatric pathology, in order to refer the patient as quickly as possible to a mental health professional. Screening tools for anxiety-depression exist and are quick to use, notably the brief PHQ-2 (Patient Health Questionnaire-2) and GAD-2 (Generalized Anxiety Disorder-2) questionnaires, which can guide clinicians towards a pathology. Finally, if there is a known psychiatric pathology, it should be treated in accordance with international recommendations, and close psychiatric follow-up should be initiated initially.

The contribution of smoking to the development of long Covid remains uncertain in these studies, with conflicting results. However, a review focusing solely on smoking and vaping found an increased risk of long Covid [80]. Concerning alcohol, the lack of significance in the results is probably due to the absence of distinction between dependence and occasional use. Structured

interviews or the use of appropriate questionnaires [81, 82] to assess consumption could have improved the results. Finally, there was no consensus on polydrug use in the two studies, with only one finding a possible association with persistent symptoms.

This review also suggested a more negative psychological experience of acute Covid infection among people with long Covid. Only one study showed a link with the presence of certain long Covid symptoms, namely lack of concentration and attention.

The pathophysiology of post-Covid syndrome remains unknown. The hypothesis of immune dysregulation is frequently put forward [59, 78, 83]. The persistence of SARS-Cov-2, in certain genetically predisposed individuals with reduced immunological capacity, could result in increased release of pro-inflammatory cytokines, leading to chronic low-grade inflammation and multi-system symptomatology. Psychological stress interacts with immune defenses via the hypothalamic-pituitary-adrenal and sympathoadrenomedullary axes [84]. This immune modulation by psychological factors could explain the results of our review.

Post-infectious syndromes have been observed with many other infections besides COVID 19. Examples include chronic fatigue syndrome following infection with the Epstein-Barr virus, and irritable bowel syndrome following infection with *Campylobacter* bacteria. What's more, three months after radiologically proven acute community-acquired pneumonia (CAP), half of all patients report fatigue, and impaired health-related

Table 4 Main results of our included studies and assessment of article quality

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
1	Subramanian et al., 2022 [35]	A total of 62 symptoms were significantly associated with SARS-CoV-2 infection after 12 weeks. The largest aHRs were for anosmia (aHR 6.49, 95% CI 5.02–8.39), hair loss (3.99, 3.63–4.39), sneezing (2.77, 1.40–5.50), ejaculation difficulty (2.63, 1.61–4.28) and reduced libido (2.36, 1.61–3.47). Among the cohort of patients infected with SARS-CoV-2, risk factors for long COVID included female sex, belonging to an ethnic minority, socioeconomic deprivation, smoking, obesity and a wide range of comorbidities. The risk of developing long COVID was also found to be increased a long a gradient of decreasing age	Depression: increased risk (aHR 1.31, 95% CI 1.27–1.34) Anxiety: increased risk (aHR 1.35, 95% CI 1.31–1.39) Eating disorder: increased risk (aHR 1.16, 95% CI 1.06–1.27) Substance use disorder: increased risk (aHR 1.15, 95% CI 1.07–1.23) Learning disability: increased risk (aHR 1.24, 95% CI 1.11–1.40) Smokers and former smokers: increased risk (aHR 1.12, 95% CI 1.08–1.15 and 1.08, 1.05–1.11, respectively) All $p < 0,05\%$	Not researched	Not researched	8/9
2	Wang and al., 2022 [36]	Probable depression (risk ratio [RR], 1.32; 95% CI = 1.12–1.55), probable anxiety (RR = 1.42; 95% CI, 1.23–1.65), worry about COVID-19 (RR, 1.37; 95% CI, 1.17–1.61), perceived stress (highest vs lowest quartile: RR, 1.46; 95% CI, 1.18–1.81), and loneliness (RR, 1.32; 95% CI, 1.08–1.61) were each associated with post-COVID-19 conditions (1403 cases) in generalized estimating equation models adjusted for sociodemographic factors, health behaviors, and comorbidities. Participants with 2 or more types of distress prior to infection were at nearly 50% increased risk for post-COVID-19 conditions (RR, 1.49; 95% CI, 1.23–1.80). All types of distress were associated with increased risk of daily life impairment (783 cases) among individuals with post-COVID-19 conditions (RR range, 1.15–1.51)	Probable depression, RR, 1.39 [95% CI, 1.19–1.63] and probable anxiety, RR, 1.47 [95% CI, 1.27–1.70] $p < 0,001$ for both: increased risk of post-COVID-19 conditions Participants with more types of distress (meaning depression, anxiety, worried, perceived stress, loneliness) were at higher risk of developing post-COVID-19 conditions (≥ 2 types vs none, RR, 1.54; 95% CI, 1.28–1.86) All COVID-19 symptoms, except for persistent cough and smell or taste problems, were more prevalent in participants with vs without each type of distress Individuals with distress at baseline reported a greater number of symptoms of post-COVID-19 condition (eg, probable depression, mean [SD] symptoms = 3.4 [2.1]; no depression, mean [SD] symptoms = 2.5 [1.7]). Symptoms of depression, symptoms of anxiety, worry, and perceived stress at baseline were associated with a 25% to 51% increased risk of having symptoms that interfered with activities occasionally to always Smoking (former and active): no significant result (confidence interval includes 1)	Not researched	Very worried about COVID-19, RR, 1.43 [95% CI, 1.22–1.68] and highest quartile of perceived stress, RR, 1.50 [95% CI, 1.21–1.86] $p < 0,001$ for both: increased risk of post-COVID-19 conditions	7/9

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
3	Grisanti and al., 2022 [37]	Clustering analysis on the most common neurological symptoms returned two well-separated and well-balanced clusters: long-COVID type 1 contains the subjects with memory disturbances, psychological impairment, headache, anosmia and ageusia, while long-COVID type 2 contains all the subjects with reported symptoms related to PNS involvement. The analysis of potential risk-factors among the demographic, clinical presentation, COVID 19 severity and hospitalization course variables showed that the number of comorbidities at onset, the BMI, the number of COVID-19 symptoms, the number of non-neurological complications and a more severe course of the acute infection were all, on average, higher for the cluster of subjects with reported symptoms related to PNS involvement	No statistical analysis performed for association with Covid long	Not researched	Not researched	8/9
4	Garjani and al., 2022 [38]	Of the 7,977 patients with MS who participated in the UKMSR COVID-19 study, 599 reported COVID-19 and prospectively updated their recovery status. Twenty-eight hospitalized participants were excluded. At least 165 participants (29.7%) had long-standing COVID-19 symptoms for ≥ 4 weeks and 69 (12.4%) for ≥ 12 weeks. Participants with pre-COVID-19 web-EDSS scores ≥ 7 , participants with probable anxiety and/or depression (HADS scores ≥ 11) before COVID-19 onset, and women were less likely to report recovery from COVID-19	Anxiety and/or depression before COVID-19 onset were less likely to report recovery from COVID-19 (aHR 0.708, 95% CI 0.533–0.941) $p < 0.05$	Not researched	Not researched	7/9
5	Craparo and al., 2022 [39]	Five classes were identified: Brain fog (31.82%), No symptoms (20.95%), Sensory disorders (18.77%), Breath impairment (17.59%), and Multiple disorders (10.87%). Women reported post-COVID-19 respiratory symptoms and multiple disorders to a greater extent than men. Hospitalized subjects were more likely to report persistent symptoms after COVID-19 than asymptomatic or home-treated subjects. Antagonism, hyperarousal, and difficulty identifying emotions significantly predicted post COVID-19 symptoms	Regarding personality traits, antagonism was found to be a significant risk factor for Brain fog (OR=0.64, $p=0.01$), Breath impairment (OR=0.65, $p=0.04$), and Sensory disorders (OR=0.66, $p=0.03$) classes Difficulty in identifying emotions: risk factor for the Multiple disorders (OR=3.87, $p < 0.001$), Breath impairment (OR=3.17, $p < 0.001$), and Brain fog (OR=2.05, $p < 0.001$) classes	Not researched	Hyperarousal was a strong predictor of Brain fog (OR=2.54, $p < 0.001$), Breath impairment (OR=2.33, $p=0.01$), and Sensory disorders (OR=2.16, $p=0.01$) classes	5/10

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
6	Tene and al., 2022 [40]	Between March 2020, and March 2021, a total of 180,759 COVID-19 patients (mean [SD] age = 32.9 years [19.0 years]; 89,665 [49.6%] females) were identified. Overall, 14,088 (7.8%) individuals developed long COVID (mean [SD] age = 40.0 years [19.0 years]; 52.4% females). Among them, 1477 (10.5%) were definite long COVID and 12,611 (89.5%) were defined as probable long COVID. Long COVID was associated with age (adjusted odds ratio [AOR] = 1.058 per year, 95% CI: 1.053–1.063), female sex (AOR = 1.138; 95% CI: 1.098–1.180), smoking (AOR = 1.532; 95% CI: 1.358–1.727), and symptomatic acute phase (AOR = 1.178; 95% CI: 1.133–1.224), primarily muscle pain and cough. Hypertension was an important risk factor for long COVID among younger adults. Compared with patients with non-long COVID, definite and probable cases were associated with AORs of 2.47 (2.22–2.75) and 1.76 (1.68–1.84) for post-COVID hospitalization, respectively. Although among patients with non-long COVID HCCs decreased from \$1400 during 4 months before the infection to \$1021 and among patients with long COVID, HCCs increased from \$2435 to \$2810	Smoking: increased risk (AOR = 1.532; 95% CI: 1.358–1.727)	Not researched	Not researched	8/9
7	De Oliveira and al., 2022 [41]	Of 439 participants, most (84%) reported at least one long COVID symptom, at a median of 138 days (interquartile range [IQR] 90–201) after disease onset. Fatigue (63.1%), dyspnea (53.7%), arthralgia (56.1%), and depression/anxiety (55.1%) were the most prevalent symptoms. In multivariate analysis, dysgeusia (odds ratio [OR] 2.0, 95% confidence interval [CI] 1.18–3.44, $P < 0.001$) and intensive care unit (ICU) admission (OR 2.6, 95% CI 1.19–6.56, $P = 0.03$) were independently associated with long COVID. Fifty percent of patients reported a worsened clinical condition and quality of life	No statistical analysis performed for association with Covid long	Not researched	Not researched	6/10

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
8	Ohira and al., 2022 [42]	A total of 90 patients with a mean age of 39.8 years were confirmed as having long COVID. The median time between diagnosis of COVID-19 and visiting our clinic was 66.8 days, and 89 patients (98.9%) were unvaccinated. Depression was the most common comorbidity (nine patients, 10.0%). The most common chief complaint was disturbance of smell and/or taste (35, 38.9%), followed by memory disturbance (22, 24.4%) and fatigue (29, 31.1%). Head MRI was performed for 42 (46.7%) patients, and the most common finding was sinusitis (four patients). Olfactory testing was conducted in 25 patients (27.8%) using a T&T olfactometer, and 14 patients (56%) had mild olfactory impairment. Of the five odors in the T & T, recognition of β -phenylethyl alcohol was most impaired	The most common comorbidity with long COVID was depression (nine patients, 10.0%, 95% CI 4.6–17.6). Eight patients (8.9%, 95% CI 3.0–14.7) had a psychiatric disease rather than depression	Not researched	Not researched	7/10
9	Bai and al., 2022 [43]	A total of 377 patients were enrolled in the study. The median time from symptom onset to virological clearance was 44 (37–53) days. A diagnosis of long COVID syndrome was made in 260/377(69%) patients. The most common reported symptoms were fatigue (149/377, 39.5%), exertional dyspnoea (109/377, 28.9%), musculoskeletal pain (80/377, 21.2%) and "brain fog"(76/377, 20.2%). Anxiety symptoms were ascertained in 71/377 (18.8%) individuals, whereas 40/377 (10.6%) patients presented symptoms of depression. Post-traumatic stress disorder (defined by a pathological IES-R score) was diagnosed in one-third of patients (85/275, 31%). Female gender was independently associated with long COVID syndrome at multivariable analysis (AOR 3.3 vs. males, 95% CI 1.8–6.2, $p < 0.0001$). Advanced age (adjusted (A)OR 1.03 for 10 years older, 95% CI 1.01–1.05, $p = 0.01$) and active smoking (AOR 0.19 for former smokers vs. active smokers, 95% CI 0.06–0.62, $p = 0.002$) were also associated with a higher risk of long COVID, while no association was found between severity of disease and long COVID (AOR 0.67 for continuous positive airway pressure (CPAP)/non-invasive mechanical ventilation (NIMV)/orotracheal intubation (OTI) vs. no O2 therapy, 95% CI 0.29–1.55, $p = 0.85$)	Active smoking (AOR 0.19 for former smokers vs. active smokers, 95% CI 0.06–0.62, $p = 0.002$): associated with a higher risk of long Covid	Not researched	Not researched	6/9

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
10	Daitch and al., 2022 [44]	Older adults were more likely to be symptomatic, with the most common symptoms being fatigue (38%) and dyspnea (30%); they were more likely to complain of cough and arthralgia and have abnormal chest imaging and pulmonary function tests. Independent risk factors for long-COVID fatigue and dyspnea included female gender, obesity, and closer proximity to COVID-19 diagnosis; older age was not an independent predictor	No significant results in multivariate analysis	Not researched	Not researched	7/10
11	Afroze and al., 2022 [45]	362 participants were enrolled in the study; the median time from the onset of COVID-19 to enrolment was 57 days (IQR 41, 82). At enrolment, after adjusting for potential confounders, the HS more often had one or more symptoms, peripheral neuropathy (PN), depression and anxiety disorder, poor quality of life, dyspnea, tachycardia, restrictive lung disease on spirometry, anemia, proteinuria, and need for insulin therapy than the non-hospitalized group (95% CI > 1 for all). Although most of these findings decreased significantly over time in HS, PN increased in both groups. The incidence of diabetes was 9.8/1000 person-month, and the new requirement of insulin therapy was higher (aOR, 6.71; 95% CI, 2.87, 15.67) among HS than the NHS. Older age, being female, comorbidity, cigarette smoking, hospitalization, and contact with COVID-19 cases were independently associated with PCS	Cigarette smoking: independent risk factor for neurological findings (peripheral neuropathy, anosmia, absent/impaired taste, tremor). (OR 1.69 95% CI 1.05–2.73)	Not researched	Not researched	7/9
12	Vásconez-González and al., 2023 [46]	Overall, 247 (54.1%) responders claimed to have long-term symptoms after SARS-CoV-2 infection. Most of these symptoms were reported by non-pregnant women (94.0%). The most common Long-COVID symptoms in pregnant women were fatigue (10.6%), hair loss (9.6%), and difficulty concentrating (6.2%). We found that pregnant women who smoked had a higher risk of suffering fatigue	Smoking: The most reported symptom was fatigue with 135 cases (6.7%) within pregnant women and (93.3%) within non-pregnant women (OR 1.430, CI 95% 0.426–4.79). However, when all symptoms were studied, no statistically significant differences between Long-COVID symptoms in smokers and non-smokers were found No statistically significant differences were found taking alcohol consumption as a risk factor	Not researched	Not researched	5/10

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
13	Frontera and al., 2022 [47]	Of 790 COVID-19 patients who survived hospitalization, 451 (57%) completed 6-month (N=383) and/or 12-month (N=242) follow-up, and 77/451 (17%) died between discharge and 12-month follow-up. Significant life stressors were reported in 121/239 (51%) at 12-months. In multivariable analyses, life stressors including financial insecurity, food insecurity, death of a close contact and new disability were the strongest independent predictors of worse mRS, Barthel Index, depression, fatigue, and sleep scores, and prolonged symptoms, with adjusted odds ratios ranging from 2.5 to 20.8. Other predictors of poor outcome included older age (associated with worse mRS, Barthel, t-MoCA, depression scores), baseline disability (associated with worse mRS, fatigue, Barthel scores), female sex (associated with worse Barthel, anxiety scores) and index COVID-19 severity (associated with worse Barthel index, prolonged symptoms)	Pre-COVID history of psychiatric disease were associated with worse mRS and Barthel scores at 6 months: OR 1.94 95% CI (1.03–3.66) P=0.040 and OR 95% CI 2.23 (1.07–4.64) P=0.032 respectively	Not researched	Not researched	6/9
14	Shukla and al., 2023 [48]	Mean age of the 679 eligible participants was 31.49 ± 9.54 years. The overall prevalence of COVID sequelae was 30.34%, with fatigue (11.5%) being the most common followed by insomnia (8.5%), difficulty in breathing during activity (6%) and pain in joints (5%). The odds of having any sequelae were significantly higher among participants who had moderate to severe COVID-19 (OR 6.51; 95% CI 3.46–12.23) and lower among males (OR 0.55; 95% CI 0.39–0.76). Besides these, other predictors for having sequelae were age (≥ 45 years), presence of any comorbidity (especially hypertension and asthma), category of HCW (non-doctors vs doctors) and hospitalisation due to COVID-19	Smoking or alcohol intake did not significantly increase the odds of having sequelae	Not researched	Not researched	6/10

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
15	Jacobs and al, 2023 [49]	After adjustment of the models for age, BMI, gender, race, and smoking, the following pre-existing conditions were statistically significantly associated with the development of PASC: asthma (OR = 1.54; 95% CI = 1.10–2.15); chronic constipation (OR = 4.29; 95% CI = 1.15–16.00); reflux (OR = 1.54; 95% CI = 1.01–2.34); rheumatoid arthritis (OR = 3.69; 95% CI = 1.15–11.82); seasonal allergies (OR = 1.56; 95% CI = 1.22–1.98); and depression/anxiety (OR = 1.72; 95% CI = 1.17–2.52). When grouping conditions together, statistically significant associations with PASC were observed for respiratory (OR = 1.47; 95% CI = 1.06–2.14); gastrointestinal (OR = 1.62; 95% CI = 1.16–2.26), and autoimmune conditions (OR = 4.38; 95% CI = 1.59–12.06). After adjustment for severity of acute SARS-CoV-2 infection and depression/anxiety, seasonal allergies (OR = 1.48; 95% CI 1.15–1.91) and autoimmune disease (OR = 3.78; 95% CI—1.31–10.91) remained significantly associated with risk for PASC	Depression/anxiety: associated with the development of PASC (OR = 1.72; 95% CI = 1.17–2.52)	Not researched	Not researched	7/9
16	Knight and al, 2022 [50]	Of those receiving the survey, 437 adult patients with different degrees of severity of COVID-19 illness responded: 77% were between 3 and 6 months from the onset of infection. In total, 34.9% had persistent symptoms, and 11.5% were hospitalized. The most common symptom was fatigue (75.9%), followed by poor sleep quality (60.3%), anosmia (56.8%), dysgeusia (55%), and dyspnea (54.6%). Predicting factors for PASC were female sex and a negative psychological impact of the disease. Age, hospitalization, persistent symptoms, psychological impact (e.g., anxiety and depression), and time missed from work were significantly associated with perception of having severe COVID-19 illness. Hospitalization was not significantly associated with PASC	Not researched	Not researched	The association between negative psychological impact was significant: 52.3% for patients with persistent symptoms and 24.5% for patients without persistent symptoms ($P < 0.001$)	5/10

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
17	Sansone and al., 2022 [51]	At first follow up (median time of 49 days since COVID-19 diagnosis) symptoms more frequently reported were fatigue (80.2%), shortness of breath (69.6%), concentration deficit (44.9%), headache (44.9%), myalgia (44.1%), arthralgia (43.3%), and anosmia (42.1%). At second follow-up (median time of 15 months since COVID-19 diagnosis) 75% patients returned to their baseline status preceding COVID-19. At first follow up males were less likely to experience neurological (OR = 0.16; 95% CI: 0.08; 0.35) as well as psychiatric (OR = 0.43; 95% CI: 0.23; 0.80) symptoms as compared to females. At first follow up, the risk of neurological symptoms increased also linearly with age (OR = 1.04; 95% CI: 1.01; 1.08) and pre-existing depression was a major risk factor for persisting dysautonomic (aOR = 6.35; 95% CI: 2.01; 20.11) as well as psychiatric symptoms (omitted estimate). Consistently, at second follow up only females experience psychiatric symptoms, whereas males exhibited significantly higher mean WAI (RC = 0.50; 95% CI: 0.11; 0.88). Additionally, neurological symptoms at second follow up were more likely in patients with pre-existing comorbidities (OR = 4.31; 95% CI: 1.27; 14.7). Finally, persistence of symptoms lasting 200 + days since COVID-19 diagnosis increased linearly with age (OR = 1.03; 95% CI 1.01–1.05) and were more likely in patients affected by pre-existing depression (OR = 2.68; 95% CI 1.60; 4.49)	1) All subjects affected by pre-existing depression complained dysautonomic symptoms (defined as a condition including fatigue, confusion, insomnia, or concentration deficits) 2) Major risk factors for long covid psychiatric symptoms was depression (aOR = 6.35; 95% CI: 2.01; 20.11) 3) Duration of symptoms 200 + days increased with pre-existing depression syndrome (aOR = 2.68; 95% CI: 1.60; 4.49) 4) No significant results for smoking	Not researched	Not researched	9/9
18	Yavuz and al., 2022 [52]	Four hundred patients were included in this study, an average of 108 + 5.12 days had passed after the onset of COVID-19. The rate of post-COVID-19 neurological involvement was 73.3%, and the top 3 most common symptoms were headache (47%), myalgia (43%), and sleep disturbance (39%). Having depression (OR: 4.54, 95% CI: 1.88–10.96), female gender (OR: 2.18, 95% CI: 1.36–3.49), hospitalization (OR: 2.01, 95% CI: 1.03–3.64), and usage of favipiravir (OR: 2.07 95 CI: 1.15–3.72) were determined as independent predictors of developing prolonged neurological symptoms	Patients with depression were higher in the PNS (Prolonged Neurological Symptom group than without PNS group ($p < 0.001$). However, the rate of smokers was lower in the PNS group than without PNS group ($p = 0.047$) Univariate analysis: not smoking increase the risk of PNS (OR 1,93, 95% CI 1,116–3,22, $p = 0,016$) Multivariate analysis: Presence of depression was determined as independent predictor of prolonged neurological symptoms after the infection (OR 4.54, 95% CI 1.88–10.96, $p = 0.001$)	Not researched	Not researched	7/10

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
19	Gutiérrez-Canales and al., 2022 [53]	We included 206 outpatients in the study. A total of 73.3% patients had persistence of one or more symptoms. The most frequent/persistent symptoms were fatigue (36.9%), anxiety (26.2%), and headache (24.8%). No statistically significant difference in the SF-36 QoL scores and the frequency of persistent COVID-19 symptoms was found when comparing the 5 and > 5 months groups, except for myalgia, which was less frequently observed in the > 5 months group after COVID-19 (26.2% vs. 14.1%, $p < 0.038$). Female gender was associated with an increased risk of persistence of symptoms (OR = 2.95, 95% CI 1.56–5.57). Having comorbidities/sequelae attributed to COVID-19 and persistence of COVID-19 symptoms were associated risk factors for poor physical component summary (PCS); on the other hand, female gender, anxiety, and depression were associated with poor mental component summary (MCS)	Smoking was observed in higher proportion of the asymptomatic group (20.5% vs. 38.2%, OR = 0.42, 95% CI 0.21–0.82, $p = 0.012$)	Not researched	Not researched	7/9
20	Hastie and al., 2022 [54]	Of the 31,486 symptomatic infections, 1,856 (6%) had not recovered and 13,350 (42%) only partially. No recovery was associated with hospitalized infection, age, female sex, deprivation, respiratory disease, depression and multimorbidity. Previous symptomatic infection was associated with poorer quality of life, impairment across all daily activities and 24 persistent symptoms including breathlessness (OR 3.43, 95% CI 3.29–3.58), palpitations (OR 2.51, OR 2.36–2.66), chest pain (OR 2.09, 95% CI 1.96–2.23), and confusion (OR 2.92, 95% CI 2.78–3.07). Asymptomatic infection was not associated with adverse outcomes. Vaccination was associated with reduced risk of seven symptoms	Lack of complete recovery was associated with pre-existing depression/anxiety (OR 2.29, 95% CI 2.06–2.55 for no recovery and OR 1.66, 95% CI 1.58–1.75 for partially recovery)	Not researched	Not researched	8/9

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
21	Fleischer and al., 2022 [55]	Patients were predominantly female, middle-aged, and had incurred mostly mild-to-moderate acute COVID-19. The most frequent post-COVID-19 complaints included fatigue, difficulties in concentration, and memory deficits. In most patients (85.8%), in-depth neurological assessment yielded no pathological findings. In 97.7% of the cases, either no diagnosis other than post COVID-19 syndrome, or no diagnosis likely related to preceding acute COVID-19 could be established. Sensory or motor complaints were more often associated with a neurological diagnosis other than post-COVID-19 syndrome. Previous psychiatric conditions were identified as a risk factor for developing post-COVID-19 syndrome. We found high somatization scores in our patient group that correlated with cognitive deficits and the extent of fatigue	Patients with a psychiatric history were more likely to report psychiatric symptoms (OR 3.5, 95% CI 1.47–8.32, $p < 0.01$), fatigue (OR 2.43, 95% CI 95 1.11–5.82, $p < 0.05$), or difficulty concentrating (OR 2.58, 95% CI 1.01–6.19, $p < 0.05$) A subgroup analysis of patients with a psychiatric history ($n = 33$) showed significantly higher total fatigue scores (110.2 ± 27.4 vs. 79.8 ± 38.0 , $p < 0.01$) compared with patients without a psychiatric history Patients with psychiatric comorbidities had a higher risk of somatization compared with patients without a history of psychiatric disorders (PHQ15 ⁷ score 14.0 ± 5.5 vs. 11.3 ± 5.5 , $p < 0.05$)	Not researched	Not researched	7/9
22	Margalit and al., 2022 [56]	A total of 141 individuals were included. The mean age was 47 (SD: 13) years; 115 (82%) were recovering from mild coronavirus disease 2019 (COVID-19). Mean time for evaluation was 8 months following COVID-19. Sixty-six (47%) individuals were classified with significant long-COVID fatigue. They had a significantly higher number of children, lower proportion of hypothyroidism, higher proportion of sore throat during acute illness, higher proportions of long-COVID symptoms, and of physical limitation in daily activities. Individuals with long-COVID fatigue also had poorer sleep quality and higher degree of depression. They had significantly lower heart rate [153.52 (22.64) vs 163.52 (18.53); $P = .038$] and oxygen consumption per kilogram [27.69 (7.52) vs 30.71 (7.52); $P = .036$] at peak exercise. The 2 independent risk factors for fatigue identified in multivariable analysis were peak exercise heart rate (OR: .79 per 10 beats/minute; 95% CI: .65–.96; $P = .019$) and long-COVID memory impairment (OR: 3.76; 95% CI: 1.57–9.01; $P = .003$)	No significant difference between long covid fatigue and no fatigue in term of proportion of smoking, use of cannabis and alcohol ($p > 0,05$) No analysis for association was done	Not researched	Not researched	8/9

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
23	Gasnier and al., 2022 [57]	One hundred and fifteen (65%) patients had at least one long COVID complaint. The number of long COVID complaints was associated with psychiatric symptoms. The number of long COVID complaints was higher in patients with psychiatric disorders (mean (m) (SD) = 2.47 (1.30), $p < 0.05$), new-onset psychiatric disorders (m (SD) = 2.41 (1.32), $p < 0.05$) and significant suicide risk (m (SD) = 2.67 (1.32), $p < 0.05$) than in patients without any psychiatric disorder (m (SD) = 1.43 (1.48)). Respiratory complaints were associated with a higher risk of psychiatric disorder and new-onset psychiatric disorder, and cognitive complaints were associated with a higher risk of psychiatric disorder	No statistical analysis with psychiatric history alone	Not researched	Not researched	7/10
24	Loosen and al., 2022 [58]	Of the 50,402 COVID-19 patients included into this analysis, 1,708 (3.4%) were diagnosed with LCS. In a multi-variate regression analysis, we identified lipid metabolism disorders (OR 1.46, 95% CI 1.28–1.65, $p < 0.001$) and obesity (OR 1.25, 95% CI 1.08–1.44, $p = 0.003$) as strong risk factors for the development of LCS. Besides these metabolic factors, patients' age between 46 and 60 years (compared to age ≤ 30 , (OR 1.81 95% CI 1.54–2.13, $p < 0.001$), female sex (OR 1.33, 95% CI 1.20–1.47, $p < 0.001$) as well as pre-existing asthma (OR 1.67, 95% CI 1.39–2.00, $p < 0.001$) and depression (OR 1.27, 95% CI 1.09–1.47, $p = < 0.002$) in women, and cancer (OR 1.4, 95% CI 1.09–1.95, $p = < 0.012$) in men were associated with an increased likelihood of developing LCS	Depression (OR 1.21, 95% CI 1.07–1.37, $p = 0.002$) turned out as risk factors for the development of LCS	Not researched	Not researched	9/10
25	Buonsenso and al., 2022 [59]	The mean age was 46.48 years (SD 7.302); 76 participants were males (49.7%), and 33 participants reported being current smokers (21.3%). Overall, 19.0% of patients reported not feeling fully recovered at follow-up, and 13.7% reported a change in their job status after COVID-19. A change in occupational status was associated with being a smoker (OR 4.106, CI [1.406–11.990], $p = 0.010$); hospital stay was associated with age > 46 years in a statistically significant way ($p = 0.025$) and with not feeling fully recovered at follow-up ($p = 0.003$). A persistent worsening in anxiety was more common in women ($p = 0.028$)	No significant results between long covid subject in term of smoking and alcohol using ($p > 0,05$)	Not researched	Not researched	7/9

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
26	Lhuillier and al., 2022 [60]	Analyses revealed that COVID-19 severity was associated with age, Black race, obstructive airway disease (OAD), as well as with worse self-reported depressive symptoms. Similarly, post-acute COVID-19 sequelae was associated with initial analysis for COVID-19 severity, upper respiratory disease (URD), gastroesophageal reflux disease (GERD), OAD, heart disease, and higher depressive symptoms	Bivariate analysis: Depressive symptom were significantly associated with post-acute COVID-19 respiratory sequelae (FDR- $p < 0,001$) Multivariable-adjusted risk ratios: No significant result ($p > 0,05$ and confidence interval includes 1)	Not researched	Not researched	7/9
27	Tleyjeh and al., 2022 [61]	Out of the 9507 COVID-19 patients who responded to the survey, 5946 (62.5%) of them adequately completed it. 2895 patients (48.7%) were aged 35–44 years, 64.4% were males, and 91.5% were Middle Eastern or North African. 79.4% experienced unresolved symptoms for at least 4 weeks after the disease onset. 9.3% were hospitalized with 42.7% visiting healthcare facility after discharge and 14.3% requiring readmission. The rates of main reported persistent symptoms in descending order were fatigue 53.5%, muscle and body ache 38.2%, loss of smell 35.0%, joint pain 30.5%, and loss of taste 29.1%. There was moderate correlation between the number of symptoms at the onset and post-four weeks of COVID-19 infection. Female sex, pre-existing comorbidities, increased number of baseline symptoms, longer hospital- stay, and hospital readmission were predictors of delayed return to baseline health state ($p < 0.05$)	Previous smoker: negative predictors of return to baseline health status (OR 1.23 95% CI 1.05–1.45 $p = 0.012$) Current smoker: No significant result ($p > 0,05$ and confidence interval includes 1)	Not researched	Not researched	9/10
28	Kidwai and al., 2022 [62]	A total of 84 patients were enrolled which had suffered from COVID out of which 51 (60.7%) had post-COVID symptoms, with fatigability 40 (48%), muscle pain 16 (19%), inability to continue the normal chores 12(14%), dry cough 11 (13%), breathlessness 10 (12%), sleep disturbance and brain fog or difficulty in concentration 11 (13%), and hair loss 9 (11%) being the common complaints. There was no positive or negative relationship between the severity of COVID infection and the presence of the post-COVID syndrome	Depression: no significant results (confidence interval includes 1)	Not researched	Not researched	5/10

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
29	Magdy and al., 2021 [63]	The frequency of depression, moderate and severe COVID-19 cases, disease duration and serum ferritin were significantly higher in the cases with post-COVID-19 pain than controls. Binary logistic regression revealed that depression, azithromycin use, moderate and severe COVID-19 increased the odds of post-COVID-19 pain by 4.462, 5.444, 4.901, and 6.276 times, respectively. Cases with post-COVID-19 pain had significantly higher NFL (11.3469.7, 95% confidence interval [CI]: 8.42–14.25) than control group (7.6465.40, 95% CI: 6.02–9.27), (P value = 0.029). Patients with allodynia had significantly higher NFL (14.96612.41, 95% CI: 8.58–21.35) compared to those without (9.1466.99, 95% CI: 6.43–11.85) (P value = 0.05)	The frequency of depression was significantly higher in cases with post-COVID-19 pain in comparison to the control group (P values = 0.027) Depression increase the odd of post-COVID-19 pain by 4.462 (95% confidence interval [CI]: 1.073–18.553) There was no significant effect of smoking and drug abuse on the occurrence of post-COVID-19 pain	Not researched	Not researched	8/9
30	Abdelhafiz and al., 2022 [64]	Three hundred and ninety-six participants filled in the survey. The mean age of participants was 41.4 years. Most participants had mild to moderate COVID-19 (81.31%). The prevalence of post-COVID-19 symptoms was 87.63%, where the most frequent symptom was fatigue (60.86%). Female sex, the presence of comorbidities, lower degree of education, longer disease duration, as well as severe and critical forms of the disease were significantly associated with the presence of post-COVID symptoms. Using regression analysis, the predictors of post-COVID symptoms were severe and critical forms of the disease and intake of antibiotics and corticosteroids for treatment of COVID-19	Smoking: no significant result for association ($p > 0,05$ and confidence interval include 1)	Not researched	Not researched	5/10
31	Ghoshal and al., 2021 [65]	At 1 and 3 months, 16 (5.7%), 16 (5.7%), 11 (3.9%), and 24 (8.6%), 6 (2.1%), 9 (3.2%) of COVID-19 patients developed CBD, dyspeptic symptoms, and their overlap, respectively; among healthy controls, none developed dyspeptic symptoms and one developed CBD at 3 months ($P < 0.05$). At 6 months, 15 (5.3%), 6 (2.1%), and 5 (1.8%) of the 280 COVID-19 patients developed IBS, UD, and IBS-UD overlap, respectively, and one healthy control developed IBS at 6 months ($P < 0.05$ for all except IBS-UD overlap). The risk factors for post-COVID-19 FGIDs at 6 months included symptoms (particularly GI), anosmia, ageusia, and presence of CBD, dyspeptic symptoms, or their overlap at 1 and 3 months and the psychological comorbidity	No significant result in terms of proportion of addiction between post-COVID-19 FGID and no FGID ($p = 0.55$)	Not researched	Not researched	8/9

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
32	Peter and al., 2022 [66]	The symptom clusters fatigue (37.2% (4213/11312), 95% confidence interval 36.4% to 38.1%) and neurocognitive impairment (31.3% (3561/11361), 30.5% to 32.2%) contributed most to reduced health recovery and working capacity, but chest symptoms, anxiety/depression, headache/dizziness, and pain syndromes were also prevalent and relevant for working capacity, with some differences according to sex and age. Considering new symptoms with at least moderate impairment of daily life and $\leq 80\%$ recovered general health or working capacity, the overall estimate for post-covid syndrome was 28.5% (3289/11536, 27.7% to 29.3%) among participants or at least 6.5% (3289/50457) in the infected adult population (assuming that all non-responders had completely recovered). The true value is likely to be between these estimates	Mental pre-existing disorders were associated with occurrence of reporting any symptom and with many different symptom cluster Smoking (particularly current smoker status) also seemed to be risk factors for several symptom cluster	Not researched	Not researched	7/10
33	Alkwai and al., 2022 [67]	Three months or more after a COVID-19 diagnosis, almost half of the respondents, 109 (51.2%), had residual symptoms. The five most prevalent persistent symptoms were fatigue (13.6%), altered sense of smell (12.7%), muscle aches (10.3%), headache (9.9%), and body aches (8.5%). When questioned regarding the return to baseline health, 152 (71.4%) answered in the affirmative. The total number of chronic medical conditions was determined as a statistically significant predictor for the delayed return to the usual state of health	No significant difference between the two groups in terms of proportion of depression, anxiety and other psychiatric disorders ($p > 0.05$)	Not researched	Not researched	8/10
34	Colizzi and al., 2022 [68]	A total of 479 patients (female, 52.6%) were followed-up for 12 months after COVID-19 onset. Of them, 47.2% were still presenting with at least one symptom. While most symptoms subsided as compared to COVID-19 onset (all $p < 0.001$), a significant increase was observed only for symptoms of psychiatric disorders (10.2%) and lack of concentration and focus (20%; all $p < 0.001$). Patients presenting with symptoms related to multiple body systems 12 months after contracting COVID-19 (all $p \leq 0.034$) were more likely to suffer from mental health domain-related symptoms at follow-up. Also, a higher risk of presenting with lack of concentration and focus 12 months post infection was found in those suffering of psychiatric symptoms at COVID-19 onset ($p = 0.005$)	Not researched	Presence of mental health domain-related (OR = 2.09, 95%CI = 1.25–3.49, $p = 0.005$) symptoms at onset increased the risk of developing lack of concentration and focus one year after contracting COVID-19	Not researched	6/9

Table 4 (continued)

N°	Author(s) and year	Main results of the study	Association between long covid and psychiatric or addiction history	Association between long covid and psychiatric symptoms at baseline	Psychological experience of infection	NOS
35	Martinez and al., 2021 [69]	Persistent symptoms at 3 and 12 months were reported by 26.5% and 13.5% of participants, respectively. Most commonly reported symptoms were fatigue, im-paired sense of taste or smell and general weakness. A history of depression or state of exhaustion, pre-existing lung disease and older age were associated with persisting symptoms	History of depression or state of exhaustion: associated with symptom persistence for more than 90 days (OR 4.16, 95% CI 1.64–10.56, $p=0.003$)	Not researched	Not researched	6/9
36	Uygun and al., 2021 [70]	Significant fatigue was detected in 56.4% (155) of participants. Female gender, history of psychiatric illness, history of psychiatric drug use, and current psychiatric drug use were significantly higher in the fatigued group than in the non-fatigued group ($p < 0.01$). In addition, the fatigued group showed significantly higher scores on all domains of the FAS and DASS-21 scales than the nonfatigued group ($p < 0.01$). Female gender and a high DASS-21 total score were predictors of post-COVID-19 fatigue	Significant differences (all $p < .001$) between the two groups in terms of gender, history of psychiatric disease, history of psychiatric drug use, and current psychiatric drug use: higher proportions in the post-Covid fatigue group	Not researched	Not researched	7/10

quality of life secondary to CAP only recovers within 6 months [85]. In the absence of an organic substrate to explain these symptoms, post-infectious syndromes are often referred to as functional somatic syndromes. The analogy between chronic fatigue syndrome and post-Covid syndrome is striking [86]. Finally, post-Covid syndrome could be, in line with the observations cited above, a functional somatic syndrome triggered in the aftermath of COVID-19 infection, and favored by pre-existing psychological distress. Anxiety and depressive disorders, particularly depression, are predictors of functional syndromes, especially in cases of chronic fatigue [87]. According to a French study conducted in 2021, most patients with persistent medically unexplained neurological symptoms after non-severe COVID-19 meet the diagnostic criteria for a somatic functional disorder according to the DSM-5 [88].

The question of a psychological etiology in the genesis of long Covid was recently investigated and published in the official medical journal of the European Association of Psychosomatic Medicine "Journal of Psychosomatic Research" [89]. These authors explained that psychological distress at the time of acute Covid infection was associated with persistent symptomatology. They also cited a British article which showed that anxiety associated with COVID-19 contributed to somatization, beyond the effect of generalized anxiety disorder, with physical manifestations that can mimic the symptoms of long

Covid (notably fatigue and gastrointestinal disturbances) [90]. The anxiety-inducing context of the pandemic may therefore also have favored this development. A question remains if the subjects affected during the first wave of the pandemic presented more post-Covid syndrome than in subsequent waves. Again, according to the authors of the publication in the *Journal of Psychosomatic Medicine*, a particular belief about the estimated severity of symptoms in the event of COVID infection predicts the onset of COVID-like physical symptoms several weeks later. Similarly, the paradox between the intensity of symptoms and the absence of any abnormality during complementary examinations raises questions. They also make the link between psychological factors and the prolongation of symptoms in the case of other infections such as gastroenteritis. They add, however, that psychological mechanism is not exclusive of other causes, as this could lead to inadequate exploration and assessment of symptoms, resulting in poor treatment and stigmatization of sufferers.

It is now well known that the symptoms of long covid are predominantly neuropsychiatric [91]. Emerging evidence points to roles for nutraceutical or adjunctive pharmacological agents targeting both immunological and neuropsychiatric pathways. In fact, according to Barlattani and al. [92], the metabotropic receptor mGluR2 has been discovered to be the mechanism by which SARS-CoV-2 is internalised in the cells of the central

nervous system. The efficacy of NAC in psychiatric disorders has already been demonstrated on its role as a precursor to the antioxidant glutathione, and its action as a modulating agent of glutamatergic, dopaminergic, neurotropic and inflammatory pathways [93]. Similarly, blood levels of LAC may be reduced in subjects with depression compared with healthy controls according to Nasca and al [94]. N-acetylcysteine (NAC) and acetyl-L-carnitine (ALC) could be an interesting potential treatment for post-covid neuropsychiatric symptoms. These results offer an interesting perspective for subjects with psychiatric comorbidity.

Another point is the encephalopathy due to acute Covid could lead to long Covid. Encephalopathy manifests clinically as delirium, subsyndromal delirium or a coma [95]. COVID-19 pneumonia is more likely to cause delirium. Compared with the usual delirium, delirium due to COVID-19 affects young subjects without comorbidities and may be favored by the severity of the pneumonia, behavioral restrictions and COVID-19 encephalopathy [96]. Encephalopathy can cause delirium due to significant complications such as neuroinflammation (with or without cerebrovascular involvement), demyelination of the brain, or convulsions [97]. This may be linked to post-acute COVID-19 syndrome or long COVID [97]. According to Michael et al. [95], a diagnosis of COVID-19 encephalopathy must comprise the following four components: 1) inclusion of a robust diagnosis of COVID-19 (ideally through confirmation of SARS-CoV-2 by a validated method or in reference to the World Health Organization [WHO] COVID-19 criteria for “probable” or “possible” disease; 2) documentation of a plausible temporal relationship between infection and symptom onset, such as that proposed by the Brighton Collaboration; 3) exclusion of alternative etiologies unrelated to SARS-CoV-2, such as primary organ dysfunction, intoxication, or primary autoimmune disease; and 4) through robust clinical examination and investigation, differentiation between brain dysfunction that is proportionate and secondary to systemic COVID-19 severity and a primary brain disease that may have a variable degree of systemic COVID-19 features.

E. Meppiel's editorial in *Neurological Practice* [98] explains that, whatever the etiological hypothesis (psychic or somatic links between somatic, psychic, neurobiological and immunity) are complex and imperfectly understood. The strength of this review lies in the fact that it is the first, to our knowledge, to focus solely on psychiatric factors associated with the onset of a long Covid syndrome. It was conducted in accordance with the PRISMA guidelines, which enabled us to reduce selection bias. A systematic review without meta-analysis was preferred due to the diversity of the studies included, the multitude of psychiatric histories sought and the

fact that the data were difficult to compare. We made an exhaustive bibliography with a qualitative synthesis of all the studies related to our subject, no matter what the outcome. Our publication bias is therefore low, even if it cannot be calculated statistically as in a meta-analysis.

Conclusion

The aim of this systematic review was to identify psychiatric and addiction risk factors for long Covid. We also sought to identify the presence of psychiatric symptoms during acute infection and their potential influence on the development of this syndrome, as well as to determine the psychological experience of the initial infection of sufferers. Following this review, a history of depression and anxiety were identified as risk factors. There was no consensus on the contribution of smoking to the syndrome. Other mental disorders and addictive comorbidities have been little studied but they would seem to play a role. Psychological symptoms during the acute phase, seem to contribute to the persistence of concentration and attention disorders and more long Covid subjects had a negative initial experience than subjects without long Covid. This review indicates that the long Covid syndrome may be linked to psychological factors, in addition to the other risk factors already identified such as obesity and diabetes. Identifying these different risk factors is important to help identify population that could benefit from preventive actions, in order to limit the incidence of this syndrome. Further studies of a population with a long Covid syndrome should be carried out to identify whether there is a high proportion of psychiatric antecedents among this population, and to better characterize them.

Abbreviations

BDI	Beck Depression Inventory
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
DSM	Diagnostic and Statistical Manual
GAD	Generalized Anxiety Disorder
HADS	Hospital Anxiety and Depression Scale
HAS	Haute Autorité de Santé
ICD	International Classification of Diseases
IES-R	Impact of Event Scale – Revised
mRS	Modified Rankin Scale
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa Scale
PHQ	Patient Health Questionnaire
PID-5-BF	Personality Inventory for DSM-5 - Brief Form
PNS	Prolonged neurological symptoms
PSS	Perceived Stress Scale
PY	Pack-years
RT-PCR	Reverse transcription-Polymerase chain reaction
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
TAS	Toronto Alexithymia scale
WHO	World Health Organization

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Authors' contributions

C.B.: Conceptualization, Writing - original draft, Writing - review & editing. A.B.: Conceptualization, Writing - review & editing. C.P.: Methodology. A.L.: Methodology, Writing - review & editing, Supervision. L.C.-P.: Writing - review & editing, Supervision.

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Data availability

The data presented in this study are available from the corresponding author, [C.B.], upon request.

Declarations**Ethics approval and consent to participate**

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Competing interests

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